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# Therapeutic Radiology

Carman Lecture[1]

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IT IS, INDEED, MOST fitting that a great name in radiology should be kept constantly before us as an inspiration. The name of Russell D. Carman is, and will be, perpetuated by his work, and without the aid of our special lectureship. We, however, as members of a great national society in which he was a moving spirit, need the constant stimulus embodied in the memory of men of the Carman ideals and vision, in order that we may carry forward the work to which they have made such great basic contributions. It is proper, therefore, that we set aside one period of our annual meeting for reflection, for contemplation of the assistance given us by our illustrious predecessors, and for review of our position on some timely general subject or problem of our specialty.

I shall not attempt a biographic eulogy of Dr. Carman. That has been most ably done by previous lecturers, gentlemen who were privileged to know our colleague and friend much better than I. However, I would like to make one observation that I believe has not been stressed heretofore. Dr. Carman was probably the first radiologist to recognize, in a practical way, the need for electing a major interest in either diagnostic or therapeutic radiology, and being governed accordingly. While he was interested in therapy, he realized that the problems of the diagnostic field, which was his chief interest, represented a full and complete sphere for his serious thought and activities. Consequently, he divided the department; and, while retaining a nominal control for administrative purposes, established, in practice and in fact, the first division of a major department of radiology into diagnostic and therapeutic sections, with separate staffs and practical autonomy for the therapeutic unit.

I should have liked to take this as a precedent for a discussion on a phase of therapeutic radiology, in commemorating a name associated almost entirely with the diagnostic field. However, that precedent has already been established, in part by two earlier lecturers and, finally, by Dr. Newell's (1) masterful and scholarly thesis of last year. I shall essay on such scientific contribution; but, instead, would like to offer for your consideration a few thoughts, and suggestions perhaps, on therapeutic radiology, as we stand at a crossroads, looking forward to a wider and more complicated field for therapy by means of the radioactive agents and equipment for the production of radiations of proved or possible value.

[1] Delivered at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Dec. 2, 1947.

Within less than a half century, therapeutic radiology has come into being and has developed into one of the great forces in medicine. The advances, while steady, have often been spectacular. Action has been the keynote throughout. It is just fifty-two years since Roentgen's discovery of the x-rays. Is it not significant of the immediate interest therein, that the fiftieth anniversary of the founding of the British Roentgen Society was celebrated last spring, and the forty-eighth annual meeting of the American Roentgen Ray Society was held this past fall? In each instance, the initial discussions were related to diagnosis, but it soon became evident that energy of possible therapeutic value was being emitted from the same source as that producing the rays of diagnostic value. In 1898, just three years after Roentgen's discovery, the announcement of the discovery of radium was made by Marie and Pierre Curie. From the meager bit of experience already accumulated with x-rays, it was but natural that some effects on tissues, from the radium rays, might be anticipated. It is probable that the well known Becquerel "burn" in 1901 hastened the trial of radium for medical purposes.

In point of time, therefore, the entire development of our present great specialty of therapeutic radiology, from its initial crude and empiric beginnings to its present scope and level of scientific accuracy and application, represents a period of not more than forty-five years.

During the earlier part of that period, the chief interest was centered about radium. X-rays, in the beginning, were of interest for their superficial biological effects; but it was not until the higher voltages of the 1920 level became available, that serious attention turned to rays produced in this manner as a possible means of influencing neoplastic tissues at depth. We are indebted to the President of this Society (2) for a very complete and practical review of early radium usage, in his 1946 Janeway Lecture before the American Radium Society. He has told us that Pierre Curie was so impressed by the medical possibilities, as suggested by Becquerel's "burn," that he gave some radium for experimental purposes to Danlos of the St. Louis Hospital, Paris. This work was of a superficial character only; and it was not until after the *Laboratoire Biologique du Radium* was established, under the auspices of M. Armet de Lisle, that H. Dominici, working in that laboratory, announced the principle of filtration for radium. Later, this great advance in practical usage was improved and published by Wickham and Degrais, associates, of Dominici. The Radium Institute of Paris was organized and built at the instigation of Madame Marie Curie (3) in 1912 and she was made Director of its Research Laboratory; but the therapeutic service, which later came to be so well known throughout the world, was not inaugurated until 1919.

Among the many historically interesting things that O'Brien has recorded from his researches into the early literature is the curious fact that the original suggestion for interstitial use of radium was made by Alexander Graham Bell, inventor of the telephone. He offered the suggestion in 1903 in a letter to Dr. Z. T. Zowers.

As early as 1903, radium was used therapeutically in the United States; and during the next two or three years, several well known names in this country became associated with the work. It is of interest that, while the first French radium therapy was for superficial lesions, the early American efforts were directed toward the treatment of carcinoma of the uterine cervix. This field still remains the one of greatest achievement for radium therapy. It is a strange coincidence that the year of the discovery of radium, 1898, is also the year in which Wertheim published his procedure for the radical surgical removal of carcinoma of the uterine cervix together with the adjacent lymph node-bearing tissues. While the method was neither original with Wertheim, nor as extensive as that now being tried in a carefully selected group of cases by Dr. Joe V.

*Photo by Pach Bros., N. Y.*

DOUGLAS QUICK, M.D.
Carman Lecturer, 1947

Meigs of this city, the Wertheim operation is the one most widely known and referred to in relation to radical surgery for this particular disease. In the intervening forty-nine years, there is little doubt of the relative value to humanity of Wertheim's surgical method and the treatment with radium.

It was not long after the simple, empiric, single-handed efforts with radium began to show encouraging effects that more completely organized and equipped investigations were launched. Kelly and Burnam, in Baltimore, were treating cases as early as 1909. In 1910, Forssell in Stockholm established a radium service. This was followed in 1915 by the establishment of a radium service, under the direction of the late H. H. Janeway, in the Memorial Hospital, New York, then recently reorganized for the purpose under the guidance of the Cornell Medical College. During the next few years, the supply of radium to that institution and at Kelly's hospital in Baltimore, was built up through the Colorado mining activities of the late Dr. James Douglas and Dr. Kelly, and by the generous support given to the Memorial Hospital by Dr. Douglas.

The use of radium advanced rapidly at the Memorial Hospital, partly because a substantial quantity of the element, together with fair laboratory facilities, was available; but largely due to the enthusiastic group engaged, whole-heartedly, in a new and fascinating project. With this group, the work with radium made steady and, I believe, sound progress. Appreciation of the influences of quality, as well as quantity, made for improvements in filtration, and a recognition of the value of distance, in delivering adequate depth doses.

In 1916, Failla was able to seal radium emanation—radon—in fine glass capillary tubes. These were embedded, interstitially, in tumor-bearing areas through trocar needles. The reactions were terrific, but there was brought about a degree of local tumor control not previously accomplished. Between 1917 and 1925, the use of these very slightly filtered "seeds" or implants, in spite of the criticism levelled at them because of the severity of the reactions, advanced the efficiency of radium therapy a good deal. I have long had a feeling that the method should be tried again, in the light of our interim experience, and with the use of weaker individual seeds. They at least went a long way toward eliminating the fallacious surface applications then so universally employed, and in calling attention to the ultimate possibilities of interstitial irradiation.

It should be pointed out that the earlier work with radium, so far as this country is concerned, was not for the purpose of furthering radium as such, or investigating it as a new element, but rather for what it might contribute toward the better handling of cancer. At the beginning of this century, the general view of cancer was a gloomy one. The only treatment, other than symptomatic terminal care, was surgery; and the only real surgical interest, of a progressive character, was sporadic. With the prospect of added benefit by radium, and aided by the then available x-radiation, it was the radiologist—then, the "x-ray man"—who injected new life into the fight for an improved cancer treatment. The more forceful his support of the crude and empiric efforts at irradiation of cancer, the more was he frowned upon by his surgical colleagues, who were grateful for his diagnostic assistance but resentful of his possible encroachment on their surgical domain. There are still far too many surgeons who regard irradiation as competitive rather than complementary to surgery. When the American Society for the Control of Cancer, predecessor of the present American Cancer Society, was a young and struggling organization, it was largely through the radiologists, rather than the surgeons, that it was able to gain support in making contact with the local communities throughout the country.

Therapeutic radiology has initiated and then supported the drive against the scourge of cancer from the beginning of popular organized efforts in that direction,

until now those efforts, by their magnitude and multiplicity, have created for this one of the great unsolved problems in medicine a status of peculiar notoriety. The propaganda needs to be shifted from the public to the public's family physician or the internist. Serious and conscientious attention to well done, periodic, health examinations would advance and improve the safeguards of the public health against many conditions, including cancer.

Those deeply and seriously interested in cancer as one of our greatest problems in medicine today, should ever be mindful of the fact that therapeutic radiology, in its kindergarten days, provided the spark to set off a new era in investigation and treatment of neoplastic diseases.

In making a brief review of the developments in the earlier years of curie therapy, for the purposes of sequence, I should like to record one bit of very crudely done work, the results of which were not published. It is of interest only because of its somewhat relationship to our present use of the products of nuclear energy. Dr. Janeway carried constantly in mind the hope that some means would be found whereby radium might be used as a constitutional agent. We were using an active deposit of radium emanation on lead foil for various unfiltered contact surface applications of short duration. Failla suggested that the active deposit be deposited on sodium chloride, ordinary table salt, then dissolved in sterile water, and injected intravenously. During 1917 and 1918, we did a modest amount of this. Dr. Failla directed the preparation of the active deposit on salt and, under Dr. Janeway's direction, I administered it intravenously in cases of Hodgkin's disease, lymphosarcoma, and the leukemias. It had a profound effect on the blood picture of the patient, as well as on the hands of the operator. It seemingly conferred some benefit in leukemia. For various and obvious reasons, however, it was discontinued and would have been entirely forgotten, were it not for the present interest in the intravenous use of the radioactive isotopes.

I have referred to the interstitial use of glass radon seeds. For several years after their introduction, they were severely criticized because of the intensity of the local reactions following their implantation. The only justification we had for continuing their use was the plain fact that they accomplished results that we were not otherwise able to duplicate. After many trials, using various metals and methods of sealing, Failla was able, late in 1924, to collect radium emanation in a fine gold capillary tube, divide it into short sections, and seal the ends so as to prevent leakage of radon. Thus the filtered radon seed was an accomplished fact. After some months of further experiment with the gold seeds, Failla turned a supply over to me for clinical use. Treatment of patients by this method actually began in June 1925. There has always been a great deal of controversy over the relative value of the gold radon seed *vs.* the more heavily filtered radium element needle, for interstitial irradiation. The greatest opposition was from the proponents of the French school. This is not the place to review the arguments, pro and con. There is, obviously, a place for each method.

Interstitial irradiation, first, and intracavitary irradiation, second, represent the most efficient general methods of radium usage. These technical adaptations of radium application provide the most efficient means, to date, of irradiating small, inaccessible, or otherwise technically complicated, tumor-bearing areas. The range of application, especially as a source of supplemental irradiation, is indeed great. It requires patience on the part of the operator and a peculiar painstaking experience which embodies some risk, in order to avail oneself of these advantages; but it is worth it. Since Failla's development of the gold seed implant in 1925, radium therapy has made substantial progress. Methods have become standardized and stabilized. The range of application has been reduced, for reasons to be mentioned shortly, but the work is on a much more rational and substantial basis. The gold-

filtered radon seed, however, was the last great spectacular development in the rapid rise of curie therapy.

X-ray therapy had been struggling along on a largely empiric and, technically, superficial-therapy basis, while radium was occupying the center of the stage. The real force, and that directed almost entirely against cancer, was radium; x-rays were of interest, but weak.

The difficulty with x-rays of the earlier period, for therapy, was largely a matter of equipment. The generators employed to activate the tubes were not powerful; but they were, at least, relatively as powerful as the tubes. About 1912, there were some fundamental researches in pure physics on the quality, as well as quantity, of x-rays; filtration and its relative value were better understood. With improvement in tubes, especially the advent of the Coolidge hot-cathode tube in 1913, the equipment to activate them improved. Research and the development of equipment for producing x-rays moved ahead apace, until the so-called high-voltage units, operating at or near to 200 kv., became available soon after 1920. For the first time, a reasonable quantity of x-rays could actually be delivered to a reasonable depth. For the first time, x-rays had something to offer by way of aiding in the control of deep-seated cancer. For the first time, the roentgenologist had within his department, and free from outside interference, an equipment of substantial power for therapeutic purposes. The psychological influence of this last fact has contributed a great deal, along with other factors involved, to create a widening gap, during the intervening years, between roentgen therapy and curie therapy.

Since the early 1920's, the progress in x-ray therapy has been equally as spectacular as was the development of radium therapy in the decade preceding. With the range of application so much wider and facilities for its use so generalized, it comes today to overshadow all therapy by irradiation, at least in its practical and proved applicability. The x-ray therapist has been guided through these years by that small group of physicists who early elected an especial interest in radiation, and whose foresight in grasping and even anticipating the needs of the clinician have made them seem, at times, to be almost intuitive. In a most able and far-seeing discussion on Training in Radiation Physics for Residents in Radiology, before the last annual conference of Teachers of Clinical Radiology, Portmann (4) paid tribute to the radiation physicists as being, undoubtedly, the best teachers of residents, in contradistinction to the majority of physicists teaching physics in institutions of higher education, who fail to grasp the practical application of their science in its relation to clinical medicine.

Along with scientific and applied research in radiation physics, clinical experience has steadily advanced and, with it all, the manufacturers have not only kept pace with demands, in most instances, but, I fear, at present have perhaps run on ahead of us. It must be said to their credit that, throughout these years of furious development of bigger and better x-ray therapy equipment, they have listened more to the physicist than to the clinician; at least they have usually awaited a nod from the radiation physicist before going ahead on a new venture.

The international co-operation in the exchange of methods, ideas, and results has been very free and has been encouraged and facilitated by the periodic meetings of the International Congress of Radiology.

Since its inauguration in 1934, the American Board of Radiology has been a powerful influence for the betterment of all radiology. This is probably more completely true of the diagnostic than the therapeutic side. However, much has been accomplished and much more can and must be accomplished in therapy.

While the dislocations of the war years tended to retard the tempo of progress in therapeutic radiology, it did hasten one phase. We were not unfamiliar with the possible therapeutic application of some of the products of nuclear energy.

We had had some very slight experience; but production of radioactive isotopes was not only difficult and expensive, but was very limited as well. This situation has been altered, somewhat, by the results of the development during the war years under Project Manhattan. The tragically spectacular atomic bomb has tended to popularize somewhat this phase of radioactivity in the public mind and in as far as its medical application may be possible.

From even this sketchy résumé, it must be apparent that a great deal has come about during the forty-five-year over-all lifetime of therapeutic radiology, of which the really active period of the specialty is little more than thirty years.

It may be well, at this time, when we are confronted by problems within and when our responsibilities from without are being added to by higher powered equipment and new sources of radioactive energy, to attempt a bit of a survey of our position. By a survey, in this instance, I have in mind our long-range plans for development. I am concerned, as we all are, with many of our unanswered or only partially answered clinical, physical, and biophysical research problems of the moment. We are all anxious about the final answers on such questions as quality of radiation *vs.* quantity, selective action, periodicity, rate and frequency of delivery, together with optimum time of over-all irradiation.

We are concerned with the greater accuracy incident to computation of all dosage on an intra-tumoral basis, and on a perfect integration of the gamma roentgen with the roentgen. About these and many other matters, I think we need not worry too much. The bright young minds coming yearly into the field, by way of the Board of Radiology and the Committee for the Certification of Radiation Physicists, will solve these problems for us, and pose new ones. My concern for therapeutic radiology at this stage is in its plans for the future and in their implementation.

The first impression I gain is that this specialty has rather outgrown its originally envisioned bounds—if, indeed, there were any. In that semi-adolescent state, it is faced with grave responsibilities, and yet hampered by restrictions and a lack of full support to meet the obligations. It very much needs today a strong, far-seeing guidance and support in order that it may develop in orderly fashion and meet successfully, not only the problems of its present scope, but those new ones already on the horizon and emanating from our new agents and equipment for the production of radioactivity of possible medical therapeutic value.

When we aim at an ideal, we must admit that many compromises will be necessary in order to make it practically operable. It is with a full realization of this, that I suggest a division of Radiology into a Department of Diagnostic Radiology and a Department of Therapeutic Radiology. The common bond of union, a transformer and an x-ray tube, has so changed in complexion, in the two spheres of activity over the years, as to be no longer recognizable.

I anticipate the first objection; namely, that few communities or institutions can support such an arrangement. I believe that most Class A general hospitals of reasonable size, can, if they live up to their moral obligations and give the most enlightened services to their clients. Beyond that, the smaller and more remote hospitals and communities will be able to have such advantages within less than a professional generation, as need for additional irradiation increases and as soon as trained personnel is available. In the meantime, the situation in these latter areas will continue to be handled by those gentlemen to whom Portmann aptly referred in the address which I have previously mentioned, as "general practitioners of radiology." They are the men covering institutions in communities where there is not, at present, enough work, even if trained men were available, to make the division. They should not be the men in larger communities, especially with more than one institution, who insist,

for competitive or other selfish reasons, on maintaining two or more second-rate therapy departments when the area could well support one department which would be both a credit and a benefit to the district.

I appreciate fully that many, probably most of the senior men, and especially those in charge of large departments, will take keen exception to my suggestion of a split in the Department of Radiology. I suspect that sentiment, more than anything else, will be the impelling force back of that objection. Some of these gentlemen have a very sincere interest in therapy, even if it is a secondary one. I am sympathetic with their feeling, but I am confident that they are fair-minded enough to favor the best interests of those in need of irradiation therapy. I hasten to explain that this is no implied criticism of what has been done thus far, or of those stalwart gentlemen who have contributed most to the development of so much radiology in so few years. Most of the contributions in both branches have been made by men who were, in reality, "general practitioners of radiology." By their very contributions, they have of necessity added to the complexity, as well as efficiency, of radiology, until we are now in need of some "special practitioners of radiology."

Diagnostic radiology, in all of its branches, is today almost more than a full-time study in itself. When therapy is added, it becomes of necessity a secondary consideration and, as such, is all too often passed over hurriedly. Therapeutic radiology is much too serious a problem, and the stakes are too great, to be passed over hurriedly. There are too many errors of omission, and casualties, these days, from hurried treatments and from the employment of treatment factors which facilitate the more rapid movement of patients through the department or office. Such procedures have their economic advantages but the economy is not on the side of human life.

As presently constituted, the average Department of Radiology thinks largely in terms of diagnosis, and but slightly of therapy. That was exemplified very nicely at the Annual Conference of Teachers of Clinical Radiology in Chicago last February. The morning session dealt largely with the teaching problems incident to diagnosis, and but little with those of therapy. In the afternoon, a discussion of training in pathology for residents made no distinction between the basic needs in diagnosis and therapy and gave no indication that the diagnostic man might profit more by a full dose of general surgical pathology, while the man inclined toward, or "majoring" in, therapy would spend his extra time more advantageously in tumor pathology.

A review of calendars of graduate training courses shows much more attention to diagnosis than to therapy. A reasonable variation on this score is to be expected, but the disparity is too great to be healthy for therapy. Furthermore, the time allotted to radium grows less and less. There are logical, even if unfortunate, reasons for this. The development of x-rays during the past twenty or more years has tended to create an improved and efficient Department of Roentgenology rather than of Radiology. The development of efficient and flexible equipment for x-ray therapy has tended to "over-extend" therapeutic roentgenology, often unconsciously, in an effort to keep therapy strictly within the department. It is always under the complete control of the roentgenologist; and besides, it is safer for the operator and does not get lost.

Radium should bear its fair share of blame for its present miscellaneous position. In the early days, the ownership or control of radium, or both, varied between institutions, special departments of institutions—not necessarily the x-ray department—and individuals. Precedents, often unfortunate ones, became established, and such prerogatives are often difficult to alter. The same method of trial and error, usually the latter, may obtain today as it did in the beginning. One of the greatest handicaps incident to this irregular

arrangement of radium control has been the pernicious habit of subleasing by the owner, whether the owner be institution or individual. I am convinced that this has been productive of more harm and damage, in the past, than all of the discrepancies of judgment that have been charged up against the reliable commercial radium companies in their leasing operations.

It is not within my province, nor indeed would I be capable of suggesting the various ways and means necessary, in so many and varied circumstances, to bring radium back under the wing of the Department of Radiology or, better still, the Department of Therapeutic Radiology, as completely as is x-radiation. It may, in some instances, require pressure; in others, time. Ultimately, however, it is essential. The therapeutic radiologist must be that, and not a therapeutic roentgenologist. If he chooses, in his adjustment of activities, to be the latter, he should at least be capable, by both training and experience, of determining and directing any necessary radium usage. To that end, an adequate supply of radium in suitable form must be an integral part of the equipment in the department. Unless the director of the department is capable of meeting his obligations on the curie therapy side, the department is not suitable for training residents in therapeutic radiology. Such men are very much needed now, and the demand is increasing. It will take time and ingenuity to bring about the re-adjustment of many departments, but it will be well worth the effort. A little of benevolent indulgence toward the occasional antagonistic head of a special service department will, ultimately, react to the advantage of both that individual and the therapy department. The occasional indifferent therapy department may need a bit of pressure. Radium fills a place in the field of radiation therapy that, so far, cannot be otherwise provided; unless it is used, and its application taught, the man in training will never know of those advantages, and the unfortunate patient is apt to become a casualty by omission. Economically, it is quite feasible to have an adequate supply of radium for all qualified therapy departments or individuals. The cost has decreased in the ratio of about 5:1 in the past thirty years. Adequate supplies are available today by either purchase or lease of the element, or purchase of radon. Details of organization must vary considerably in institutions, and depending on personalities, interest of available specialists, and association or not with a tumor clinic. Co-operative effort will solve these problems. The important feature is to have the radium a part of, and controlled by, the therapy department. It should not be loosely and miscellaneously spread about.

I have no sympathy with the idea of government control of medicine. However, it is interesting to note that the requirements of the National Radium Commission and the Medical Research Council of England, for usage of radon supplied from centers under their control, are much more rigid than we adhere to in this country. They sound very reasonable. The application is limited strictly to trained and qualified physicians. It is to be hoped that the regulations do not run afoul of too many politicians.

It may be a bit surprising to some that I have favored a compact and complete department for radiation therapy, rather than therapy controlled by a cancer expert. There are two reasons for that decision. Besides, I might counter with the suggestion of special training in cancer surgery for the therapeutic radiologist, were it not that his prospective responsibilities for some time ahead are already more than full. Even at that, it is imperative that he have at least a substantial clinical knowledge of cancer and of tumor pathology.

There was a time when I would have favored placing therapeutic radiology under the clinical cancer specialist, even splitting the therapy, perhaps, between the special departments of cancer management. Time and experience rather sug-

gest that the cancer therapist or cancer specialist is too changeable to be vested with any such responsibility. Cancer institutes and special cancer hospitals are very necessary in our present medical and institutional framework. They have been known, however, to follow trends. Their trends, for a time at least, carry weight. The advantages of modern surgery make one more trial of ultra-radical surgery look very tempting to the young cancer clinician with a surgical training. An institution dominated by his zeal would, ultimately, contribute an ample material to therapeutic radiology, but would it contribute to improving the efficiency and administration of that therapy? It would probably be safer to increase the radiological requirements in that young man's training and then have him examined for certification as a cancer clinician by a therapeutic radiologist.

In special cancer hospitals with a large clientele, and in general hospitals, particularly teaching institutions, with large radiation therapy departments, would it not be advantageous to have two therapy services instead of the traditional single service? The principle of friendly competition might be a worth-while stimulus. It has been so, in the past, in the organization of medical and surgical departments.

The other reason for establishing, maintaining, and developing a major department of therapy by irradiation on its own recognizance, and free from shackles of influence, is the fact that this specialty, today, covers a good deal more than the irradiation therapy of neoplastic diseases. More attention is constantly being given to some of the infectious, inflammatory, and functional diseases. The super-voltages of the cyclotron, betatron, and synchrotron will alone require the guidance of a super-therapist. The same applies to the possible medical uses of the many and increasing products of nuclear energy. If materials of such potentialities are allowed free range among those who would gladly toy with them, the unhappy results might very well eclipse some of the earlier experiences with x-rays and radium. The potential personal dangers, even to experienced operators, with the powerful radiations being used and contemplated at this time, make an ever increasing rigidity of control imperative. That control should be placed and remain where a painful experience at the lower levels of radiation potential has already been accumulated.

Time and experience will determine the various off-side contacts and relationships of such a broad basic general department of therapeutic radiology. It may very well be advisable to make different co-operative arrangements with different specialty departments, depending upon their peculiar needs. For example, the character of the irradiation employed in dermatology differs so completely from that employed elsewhere, that the question of autonomy, or rather continued autonomy, arises. If such is to be extended, would it not be advisable to restrict malignant lesions of the skin to the department of therapeutic radiology, at least in the absence of a special tumor clinic? The relationship between the therapy department and the tumor clinic will be worked out over a period of time; friendly co-operation will solve the differences. With the proper co-operation established between the therapy department and the various special services using some radiation for a definite part of their work, it is conceivable that a few years hence might see the therapy section of the American Board of Radiology aiding in the irradiation therapy certification as a special service to other Boards whose diplomates have some active contact with radiation in their one particular branch of practice. At present, it is doubtful if the examinations in their phase of therapeutic radiology mean much.

Regional or community planning has had a good deal of popular support and will probably be a factor of increasing importance in the development, alteration, or replacement of existing hospitals in the larger cities. The New York City Planning Commission made public a compre-

hensive "master plan," which included a hospitals plan, earlier this year. Other cities are doing the same. The American College of Surgeons has very complete plans, and stipulations of minimum standards, for various types of cancer clinics. Through such studied planning, does it not seem that a more orderly development of departments of therapeutic radiology may be anticipated and a more efficient integration with special service departments and tumor clinics looked forward to?

Equipment and facilities for this type of work are unfortunately expensive and are becoming more so. It is rather obvious, therefore, that all institutions cannot hope to have the same degree of perfection in the organization of the department of radiation therapy. The central units in a master plan, and those strategically located otherwise, should of necessity be the complete or ultra-equipped units. From that level, degrees of completeness in equipment may perhaps have to be graded down the scale to the smaller institutions and those more remotely located. It will necessitate some shifting of patients among those in need of very specialized care. On the other hand, all routine treatment of ordinary type and grade should be amenable to care in the nearby institution.

In private practice, the same gradation in facilities and integration of the work might reasonably be anticipated and governed, for the most part, by the capabilities of the practitioner. As the trend goes in our institutional development, so is it likely to proceed in outside private practice.

In suggesting recognition of a division in radiology, and thus giving formal blessing to an autonomous department of therapeutic radiology, it must be realized that there is nothing about it to be legislated. If the time is ripe for recognizing a division or separation of responsibilities, the new department must be so dignified as to attract some, at least, of the best minds going into radiology or some of the best minds going into clinical cancer. Such individuals are not going to be satisfied or happy with anything less than the freedom of a major autonomous department. It is one of those changes that must come about largely through the influence and action of the professional conscience of the radiologist. There are, perhaps, a few things that might be done to encourage or activate that conscience.

The first step might, quite properly, come from the American Board of Radiology. It is the institution charged with the setting of standards and certifying to the fitness of candidates as judged by those standards. It has long been recognized within that Board that proficiency in roentgen therapy does not qualify a man for unrestricted endorsement in radiation therapy. However, it is very apt to be so misinterpreted by the candidate once he has been certified and, unfortunately, by a large section of the profession and the lay public as well. The Board has been hesitant about taking a stronger position because of the limited facilities for training in radium therapy. Nothing short of the insistence of the Board will change this indifference to the establishment of adequate training in curie therapy by the departments charged with or assuming responsibility for training residents in therapeutic radiology. The law of supply and demand may very well be reversed and interpreted as demand and supply. Several years ago, the Board eliminated radium therapy, alone, as an adequate or acceptable basis for certification. In 1943, Dr. George Holmes (5) suggested a revision or simplification of the groupings for certification which, in effect, would eliminate roentgen therapy alone as an adequate basis for a therapy approval. He suggested three classes only as acceptable for Board certification, *viz:* radiology, diagnostic radiology, and therapeutic radiology (which includes both x-ray and radium therapy). It is to be hoped that this suggestion from the conservative dean of American radiology will soon be accepted. The major responsibility of therapy by irradiation is still

directed toward the relief of cancer. It is a serious responsibility. The least we can do is to provide and insist upon a full and complete training before endorsing the assumption of such an obligation.

The American College of Radiology has done a very great deal during the past few years to improve the position of radiology in the general field of medicine. The welfare of radiologists, both individually and collectively, has been its constant responsibility. When radiology is willing to make another advance by accepting therapy as a major specialty, there is no doubt but that the experience and good offices of the College will be of invaluable assistance in setting up and guiding the additional organization and integration that will be found necessary.

Question will at once be raised as to how additional trained personnel in therapy is to be supplied. That is a problem for those who assume the responsibility for training in therapeutic radiology, and within the limitations of their teaching facilities. By way of reassurance, it should be pointed out that the program is of necessity a gradual development: no overnight shift is being suggested. It does not mean an entirely new and additional group of post-graduate students or residents. Some would simply be electing therapy entirely and, thereby, relieving the pressure on otherwise diagnostic or general radiology students. As more men are trained and certified, it means that they contribute toward more facilities for the training of additional numbers of candidates. Since the demand for training exceeds the facilities, care should be exerted in selecting the candidates so that the scarce and valuable training facilities will not be wasted.

With all of that, however, the demand for training will, for some time, be greater than the available facilities can provide. Every effort, by combinations and otherwise, should be made to afford the maximum of facilities, at least until the backlog has been met. As Dr. Holmes (6) pointed out in his Carman Lecture on "The Development of Post-Graduate Training in Radiology," there are many hospitals in which some branches of therapy (as well as diagnosis) may be obtained, but in which all phases of therapeutic radiology are not covered. It may even be advantageous for the trainee to spend the required "pre-Board" years in two or more institutions rather than in one place only. The Professor of Radiology at Harvard, Dr. Merrill Sosman, is blazing the trail in this direction, and by election rather than of necessity, by having his residents spend part of their time in two or more additional institutions. While this plan is for the general training in radiology, I believe the doctor visualizes an extension of the same principle to augment the special training in therapy.

The preceptor, as an acceptable part of the training program, is not in favor. That, in a measure, is readily understandable. However, is not the pathologist or the physicist a "preceptor"? Why not then the clinical radiation therapist? It ought to be possible to select an acceptable group from those not engaged in institutional departments and thereby augment the training staff.

Another intriguing possibility for enhancing the training program, at least in a semididactic manner, is suggested by the proposal of a Registry of Radiological Pathology in the Army Institute of Pathology at Washington. While the original plan was for diagnostic radiological pathology, there is no reason why therapy material could not also be assembled. From that material, in turn, departments throughout the country could borrow, to supplement the weak points of their own facilities. This might be of especial interest to those therapy departments that are weak in radium therapy and that find the development of that phase of their work temporarily hampered. It is not suggested as a replacement, but it might be a help.

With the ideal of better and more complete service ever before us, and supported by the demands of the constituted authorities in our field, progress in the training

and practice of therapeutic radiology will be accomplished.

The progress to which we ordinarily strive and refer is that which is based on greater scientific accuracy and application. It is, as a habit, a part of our times. In applying the advantages of our scientific attainments, we must not forget to do so as physicians and not merely as technicians. The art of medicine occupies quite as significant a place as does the science in the care of the sick, especially those suffering from the more serious diseases. There is too much tendency on the part of those in some of our large teaching institutions to brush off that phase which we refer to as the art of medicine, as being within the sphere of private practice only. They forget that most of their science is based on an original premise and that often, only through interim breeding, does it become a "fact." They fail to recognize that the dependent or indigent on the ward is just as much benefited by the kindly and understanding application of the high-powered treatment as is the private patient in the upholstered office. It is possible that even scientific accuracy can be over-estimated. In his autobiography, Hans Zinsser (7) tells us that he was once so reminded by a Scandinavian fishing-boat captain. In last year's Carman Lecture on "Quality of Radiation in Roentgen Therapy," Dr. Newell (1) was not too much impressed by the relative values of varying qualities of radiation, and concluded with the following comment: "But I still don't see very clearly how one quality is going to be better able than another to ferret out the cancer cell." Upon the occasion of his elevation to the Presidency of the British Roentgen Society, for its fiftieth year, D. W. Smithers (8) delivered an erudite and semiphilosophic address on "The Radiotherapist and the Cancer Patient." Among other things in similar vein, he said, "How do we judge ourselves? By classification, standardization, and the calculation of survival rates? Or, by the comfort of mind, relief of bodily distress, and continuation of useful and pleasant existence that we help each patient to achieve."

In his Janeway Lecture, Dr. O'Brien (2) has told us that "the technique of the Institut du Radium de Paris was not given in terms of dosimetry, according to Regaud, but in terms of accurate observation of the biologic effects (experience) and with emphasis on the complex physical, geometric and radiophysiologic factors, because the dose in radiotherapy is not the simple and almost independent factor which it is believed to be by common error." (Experience, rather than slide-rule.)

Another danger of too much dependence on scientifically accurate treatment alone lies in the failure to recognize the advantages to be derived from progress in other fields of medicine. The effects of radioactivity in tissues may be tremendously enhanced by the aid of the antibiotic drugs, under certain circumstances. In the course of interviewing rather intimately, each year, a hundred or more young radiologists recently trained in our best institutions, I never cease to be shocked by the number of them who have no realization of the value of the anti-anemic group of drugs, the essential vitamins, and some hormones, as aids in meeting the problem in which they are otherwise completely absorbed. In this direction alone, there is opportunity for a great deal of original investigation and advancement. The therapeutic radiologist needs to be a very able general practitioner of medicine, as well as a special practitioner of his branch of radiology. There is so much to be accomplished in so many directions.

Perhaps, for some of us, an excellent philosophy is embodied in another reference to that grand gentleman and beloved Harvard professor, the late Hans Zinsser (7), who said, "Our task, as we grow older in a rapidly advancing science, is to retain the capacity of joy in discoveries which correct older ideas and theories, and to learn from our pupils as we teach them. That is the only sound prophylaxis against the dodo-diseases of middle age."

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SUMARIO

**La Radiología Terapéutica**

En menos de medio siglo, la radiología terapéutica ha cobrado vida, convirtiéndose en una de las fuerzas más grandes de la medicina. Durante la primera parte de dicho período concentróse la atención en el radio, pero desde poco después de 1920, el adelanto en roentgenoterapia ha sido tan teatral como lo fuera el de la curieterapia en el decenio anterior.

Dadas las graves obligaciones que incumben hoy día a la especialidad radiológica, conviene dividirla en dos Departamentos: uno de Radiología Diagnóstica y otro de Radiología Terapéutica. En el último se hará un hincapié más adecuado en la curieterapia que el que recibe ahora generalmente. El radiólogo terapéutico o radioterapeuta no debe ser un mero roentgenólogo, sino que, por su preparación y experiencia, debe ser por lo menos capaz de determinar y dirigir todo uso necesario de radio, para lo cual un abasto adecuado de este elemento formará parte integrante de la instalación del Departamento de Radiología Terapéutica, bajo cuyo control se hallará.

Discútense aquí los problemas comprendidos en el adelanto mencionado, en particular en cuanto a organización hospitalaria, certificación (diploma) por la Junta Americana de Radiología y plan de adiestramiento. Señálase, por fin, que al aplicar los resultados de los progresos científicos, el radioterapeuta no debe olvidar que lo hace como médico y no meramente como técnico. Para ello, debe apreciar la importancia que reviste la aplicación humanitaria y comprensiva del tratamiento que está preparado para administrar, a la vez que reconoce las ventajas derivadas de los adelantos logrados en otras ramas de la medicina. El radiólogo terapéutico tiene que ser un profesante muy capaz de la medicina así como un técnico especializado en su rama radiológica.

# Roentgen Treatment of Multiple Myeloma[1]

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MYELOMA IS essentially a malignant tumor of the bone marrow, which may present itself in single or multiple foci and tends to involve notably the ribs, spine, skull, and pelvis. The individual tumors develop from the primitive cells of the hemopoietic system and have been accorded a variety of names, as erythroblastoma, plasmocytoma, myelocytoma, and lymphocytoma. In the later stages of the disease, myelomatous deposits may appear in the liver, spleen, and lymph nodes—rarely in the lungs and other viscera (12).

It was our clinical impression that these lesions were not particularly radiosensitive. Therefore, it was with some interest and surprise that we recently noted statements from two authorities to the effect that myeloma was regarded as a *very radiosensitive* lesion. Shields Warren (30) observed in February 1947 that "multiple myeloma is a radiosensitive tumor—to be classified with lymphoma and Ewing's tumor of bone!" In the same year del Regato (1) wrote: "Myelomas are very radiosensitive and locally radiocurable." In view of these observations, we decided to re-examine the recent literature and to review the cases of multiple myeloma which we had been privileged to see in the radiation therapy department at the San Francisco Hospital during the last two decades.

## INCIDENCE

Multiple myeloma is a rare disease. Batts (3) reported 40 cases in a survey of almost 300,000 admissions to the University of Michigan Hospital. Bayrd and Heck (4) reported 83 proved cases out of a total of 350 with a clinical diagnosis of multiple myeloma, obtained from *all* patients admitted to the Mayo Clinic up to the year 1946. Ehrlich (10), in a ten-year period at the New York Cancer Institute, saw 7 cases among some 127 primary bone tumors; only 3 of these were verified microscopically.

The sexes are involved in a ratio of approximately 1.5 males to 1 female. The incidence is highest between the ages of forty and seventy years, but the disease has been reported in persons as young as sixteen months and as old as seventy-eight years.

| *Author* | *Average Age* |
|---|---|
| Geschickter and Copeland | |
| Collected cases | 55 (most cases 40–70) |
| Batts | |
| 40 cases | 53 (most cases 28–73) |
| Bayrd and Heck | |
| 83 cases | 57 (most cases 37–78) |

## PATHOLOGY

Myelomatous tumors are usually gelatinous in appearance and from red to gray in color. Codman (8) in 1925 subdivided them into lymphocytic, myelocytic, erythroblastic, and plasma-cell types. Longcope (18) in 1927 added a fifth, the myeloblastic. The plasmocytomas are the most frequent and the erythroblastomas probably the least so. Wintrobe (31) has pointed out that the plasma cells of the myelomas differ in certain respects from ordinary plasma cells. The chromatin of the nuclei of the cells of the plasmocytic myelomas does not show the characteristic "spoke-wheel" arrangement, and the perinuclear clear areas seen in true plasma cells are hardly ever observed. The tumor cells have no osteoclastic or osteoblastic properties. They form small nodules which

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Dec. 1–5, 1947.

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grow by expansion and tend to necrosis and hemorrhage. The abnormal plasma cells almost always are found in the sternal marrow even in patients with apparently solitary myeloma (Bichel and Kirketerp, quoted by Snapper, 26). Lichtenstein and Jaffe (17) believe that cellular subclassification of myelomas is not warranted, and that the disease is essentially of unitary cellular type, the cytologic variations reflecting stages in the maturation of the basic tumor cell.

Metastases are found in the lymph nodes, spleen, liver, and other viscera, though very rarely in the lungs. Involvement of the kidneys, adrenals, and almost every other organ has been occasionally noted (17). Amyloid deposits are not infrequent.

*Relationship to Solitary Myelomas:* Schinz and Uehlinger (25) believe that multiple myeloma is primarily a solitary tumor, which, however, is usually seen in the multiple stage on account of its tendency to metastasize to other bones. Toth and Wintermantel (29) stated in 1943 that 48 cases of so-called solitary myeloma had been reported and only one-fourth of these remained solitary after four years. There are two main types of solitary lesion, the osteolytic type and the giant-cell type. The lesions of the osteolytic type are sharply demarcated and show little if any expansion. They are usually found in a single vertebra or shaft of a long bone, and must be differentiated from *metastatic carcinoma* and other bone-destructive conditions. Lesions of the giant-cell type are multilocular and osteolytic, with sharp demarcation and occasional expansion; they must be differentiated from *giant-cell tumors* and *fibrocystic disease of bone.*

## CLINICAL ASPECTS

The onset of the disease is usually insidious, with a period of malaise and gradually failing health as the earliest manifestation.

*Pain:* The first dominant symptom is pain, usually of a vague, wandering or "rheumatic" type, often in the lower back and pelvis. The type, location, and duration of the pain are not characteristic. At times it is sudden in onset, especially when associated with a pathological fracture. Geschickter and Copeland (11) describe a pain cycle consisting in moderately severe pain at first, followed by a remission, and later by recurrence, approaching maximum severity in the terminal stages of the disease.

*Tumor Formation:* Palpable tumors, usually on the skull and trunk, were found in 50 per cent of Batts' cases (3), but in only 12 per cent of Bayrd and Heck's (4), both series being made up of multiple myelomas. Tumor formation may be the initial symptom that calls attention to the disease.

*Pathological Fracture:* Pathological fracture occurs frequently and is often the presenting complaint. Geschickter and Copeland noted that among bone tumors, pathological fracture is most commonly encountered in multiple myeloma, then in decreasing order in bone cysts, metastatic carcinoma, giant-cell tumor, and finally sarcoma. In multiple myeloma, the majority of the fractures occur in the spine and ribs, in contradistinction to pathological fractures in the long bones in other types of bone tumor, perhaps because the myelomatous deposits are more frequent in the flat bones.

*Neurologic Manifestations:* Compression fractures of the spine may produce a sudden or gradual paraplegia. Radicular pain is among the most common signs of multiple myeloma. Scheinker (24) believes that the frequent pains of patients with myeloma may be partly due to a "polyneuritis caused by the absorption of toxic substances from the myelomatous tissue." He designated this polyneuritis as sclerosing interstitial perineuritis. Geschickter and Copeland (11) found neurologic involvement in about 40 per cent of cases, and Bayrd and Heck (4) in about 14 per cent.

*Miscellaneous Features:* Weight loss, anemia, abnormal bleeding, or renal symptoms may be the presenting complaint.

The disease may progress slowly or rapidly; long remissions may occur, rendering evaluation of therapeutic procedures quite difficult. Most patients die of cachexia, or of intercurrent infections, or renal or cardiac failure, or amyloidosis.

### LABORATORY STUDIES

*Proteins:* The incidence of Bence-Jones proteinuria varies greatly.[3] Batts found it in 50 per cent of his 40 cases, Geschickter and Copeland in 65 per cent of a large group (over 400 cases), and Bayrd and Heck in 67 per cent of 83 cases. The average incidence is probably 60 per cent. The blood protein (notably the serum globulin) is often increased.

*Blood calcium* may be normal or elevated. Gutman and co-workers (13) found it elevated in 44 per cent of their cases; Bayrd and Heck in 20 per cent; Lichtenstein and Jaffe in 50 per cent.

*Inorganic phosphorus* is rarely decreased and in the terminal stages may even be increased; the alkaline *phosphatase* content of the serum is seldom increased; the acid phosphatase is normal.

*General Blood Findings:* The hemoglobin, red cell count, total white count, and differential count are often within normal limits, but anemia tends to develop as the disease advances. Occasionally myeloma cells enter the blood in sufficient numbers to give a leukemic picture (so-called plasma-cell leukemia).

*Sternal Bone Marrow Findings:* The presence of myeloma cells in the sternal marrow is usually diagnostic of the disease. However, since these tend to lie in clumps or nodules, a negative aspiration is possible even in a definite case of multiple myeloma. Myeloma cells are large atypical plasma cells, with deep purple-staining nuclei and pale blue, faintly vacuolated cytoplasm. Some are multinuclear; others have a perinuclear halo; some show signs of amitotic nuclear division.

*Bone and Soft-Tissue Tumors:* Biopsy of tumors in the bones and soft tissues will reveal myelomatous deposits.

*Roentgen Findings:* Roentgenograms of painful areas or sites of fractures in the early stages of the disease may reveal minimal decalcification of the bone, with no characteristic findings to permit differentiation from osteomyelitis, or from primary or metastatic bone tumor. The subsequent pathologic changes may develop slowly or rapidly. A single focus may be apparent for many months, or rapid development of multiple bone lesions may ensue. These multiple lesions may or may not be symptomatic. In typical and especially in advanced cases, there are multiple sharply demarcated circular areas of destruction in the skull, ribs, pelvis, and other bones. Some patients die with few or no bone lesions demonstrable by x-ray examination.

The differential roentgen diagnosis in the early stages of the disease is usually impossible. We have seen cases, which eventually proved to be myeloma, diagnosed by experienced radiologists as simple fracture, Hodgkin's disease of bone, hyperparathyroidism, metastatic carcinoma, and osteomyelitis. Conversely, cases of osseous leukemia, lymphoblastoma, tuberculosis, carcinosis, and hyperparathyroidism may be erroneously diagnosed (from bone films alone) as multiple myeloma. Metastatic mammary carcinoma and osteomalacia are probably the most fruitful sources of confusion.

### X-RAY TREATMENT OF MULTIPLE MYELOMA

*(Review of the Literature)*

A review of the literature on the x-ray treatment of multiple myeloma has not been very informative. Most articles merely mention irradiation as one form of

[3] In 1848, Bence-Jones (6) discovered a special protein in the urine of a patient suffering from a bone disease which caused softening and fragility of the skeleton (*mollities ossium et fragilitas*). In 1873, von Rustitsky (23) described multiple tumors of bone consisting of proliferating bone-marrow elements which erode the cortex and at times penetrate into the soft tissues. In 1889, Kahler (15) concluded that the two findings existed together and described a clinical syndrome which bears his name and is characterized by deformation and abnormal fragility of the bones, bone pains, cachexia, and the presence of Bence-Jones protein in the urine. Subsequent experience has shown that this protein is occasionally found in patients with other types of bone destruction.

therapy. Belden (5) reported a case in which treatment with x-rays resulted in relief of pain only. The technic used and dose given were not stated. Stone (28) reported a similar case without technical irradiation data. One of Meyerding's patients (19) received "x-ray treatment," but no further information is available.

There are, however, some fairly complete references in the literature to solitary myelomas treated with x-rays. Bailey (2) recorded a case followed for seven years in a female 65 years of age who had progressive pain in the right arm for one year and impairment of function for six weeks. She was otherwise in excellent physical condition. The blood count was within limits of normal and the urine was negative for Bence-Jones protein. The biopsy diagnosis was plasma-cell myeloma. The patient was given "2.5 erythema doses, 140 kv., 12 doses in two weeks." After six weeks, "three skin units" of the same type were given. Roentgenograms six months later showed deposition of lime salts, with the bone assuming a normal appearance. Films made after six years did not reveal any definite evidence of disease.

Peyton (20) described a 42-year-old male with spastic paralysis of the lower extremities, loss of pain sensation below the level of T7, bilateral ankle clonus and spinal mass reflex in the lower extremities. X-ray examination showed compression and rarefaction of T6. The disk between T5 and T6 was almost obliterated. Laminectomy was performed, exposing the cord throughout the length of the tumor, about the height of one vertebra. Microscopic examination revealed plasma-cell myeloma. Eleven radium needles (65 mg.) were inserted into the tumor and left for twenty hours, giving a total dose of 1,300 mg. hr. with 0.5 mm. nickel steel as filter. X-ray therapy was started thirty-five days later. Four treatments in six days, 132 per cent of a skin erythema dose, were given to an anterior and the same dose to a posterior field (200 kv., 1 mm. Cu plus 4 mm. Al filter, 50 cm. anode-skin distance). Four months after operation the patient could walk without crutches; eighteen months after therapy he was still symptom-free.

Boidin *et al.* (7) reported a case of osseous myeloma in which two large ulcerated and infected tumors on the head involved the calvarium. The tumors were large, 10 cm. thick and 47 cm. in circumference at the base. They were treated with a coil of Robiquet (25 cm. spark; 6 mm. Al filter, and an anode-skin distance varying from 30 to 50 cm.). At each point treated, 500 to 1,000 "R" were given, repeated in the beginning every eight days, then every fifteen days. The treatment continued at intervals for sixteen months. The disappearance of the tumor was rapid, but it took months for the bone to regenerate. Lacassagne (16) had one seven-year "cure" in 12 irradiated cases; the fate of the other 11 is not ascertainable.

Batts (3) reported 23 cases of multiple myeloma treated with x-rays, with the following general technic: high-voltage radiation, filter 0.9 mm. Cu, 50 cm. anode-skin distance, area varying from 100 to 400 sq. cm., 200 r dose and 600 r to each area. Pain was definitely relieved in 78 per cent of the cases, and there was improvement in paraplegia in 4 out of 5 cases. For patients receiving x-ray therapy the average duration of life after admission was *twenty-three months* (23 cases), in contrast to *6 months* (17 cases) for those not receiving radiation.

Toth and Wintermantel (29) report a case of a solitary myeloma with survival six years after the first appearance of symptoms. The patient was a 53-year-old white female with pain in the right hip and thigh and inability to walk, which had been progressive for five years. Roentgenograms showed "primary malignant bone tumor." The lesion progressed for the next year and a half without involving the lungs. X-ray examination of the pelvis at that time revealed advanced destruction in the right innominate bone. Irradiation was started on Oct. 31, 1941—150 r on the skin (to a field 20 × 20 cm.)—and "caused a marked febrile reaction." The skin dose was then reduced to 80 r. Fifteen treatments were given, totaling 1,700 r through

three portals (200 kv.p., 20 × 20 cm. area, 50 to 70 cm. anode-skin distance; h.v.l. 2.0 mm. Cu). Roentgenograms made two months later showed no change. A second course of x-ray therapy comprised thirteen treatments totaling 1,700 r. The unusual febrile reaction was again noted. Films six months after admission showed considerable trabecular recalcification at the site of the previous destruction. Another film two months later revealed further improvement of the pelvis, but the thorax showed numerous osteolytic lesions in the ribs, with two healing pathological fractures. Tests for Bence-Jones protein were first positive on Oct. 24, 1942, and the patient died on Oct. 28, 1942, one year after radiation therapy was commenced and six years after the first appearance of symptoms in the right hip. Histologic examination of the irradiated area revealed the presence of normal bone as well as osteoid tissue. The marrow spaces were fibrotic in most areas, with occasional remnants of tumor cell collections.[4]

Pohle (21) states that irradiation is the method of choice and is best given by the protracted-fractionated method with small fields to avoid general reaction and leukopenia. "As myeloma is very radiosensitive, a total dose of 900 to 1,200 r in single doses of 180 r and distributed over ten to fourteen days, should be a sufficient amount of irradiation. Smaller areas of bone involvement may be treated by a single dose of 600 r."

Coley (9), using toxin treatment alone, had 1 patient free from disease for five years and another for four and a half years. With irradiation plus toxin, symptoms and clinical signs disappeared completely in 6 cases. With irradiation, 1 patient was symptom-free for four years, and then had a recurrence with paraplegia; at that time toxin was used and an apparent cure was obtained for two and a half years. With irradiation alone, myelomatous foci "disappeared" in 4 cases, for an unspecified number of months.

[4] Note that tumor cells persisted despite fairly heavy dosage.

Reinhard and his associates (22) did not find one case in which there was convincing objective evidence of improvement after radiophosphorus therapy. One patient had relief from pain, but radiophosphorus could not be positively identified as responsible for this. Radiophosphorus was believed to have significantly shortened life in 2 patients by producing a severe leukopenia and thrombopenia. Radioactive strontium has been used (4) but nothing definite has yet evolved.

Hall and Watkins (14) used radioactive phosphorus combined with x-ray therapy in one case of multiple myeloma, with apparent re-ossification of the tumor sites. However, they warn against the danger of permanent hemopoietic damage from oral or parenteral irradiation.

Snapper (27) has used "stilbamidine" and "pentamidine" in conjunction with a low animal protein diet in patients having multiple myeloma. Pain was favorably influenced but relapses occurred. No cases were cured. Snapper believes, on the basis of 3 cases, that some patients "refractory to x-ray treatment may become susceptible to irradiation after the use of stilbamidine."

### AUTHORS' SERIES

Since 1928 we have had in the San Francisco Hospital 18 traced cases of multiple myeloma, 11 with positive microscopic proof and the other 7 with sufficient clinical, laboratory and x-ray evidence to warrant acceptance of the diagnosis. The average age at the time of diagnosis was 53.1 years, the range being from 31 to 72 years. There were 11 males and 7 females. One patient was colored; the rest white.

The average duration of life after the diagnosis was established was 8.5 months in the proved cases, excluding one patient who has lived over nine years. Still excluding this latter unusually favorable case, the average survival in the *x-ray-treated* group was 10.4 months, in contrast to 2.3 months in the untreated group.

*Admission Diagnoses:* Some patients were referred to the San Francisco Hospital

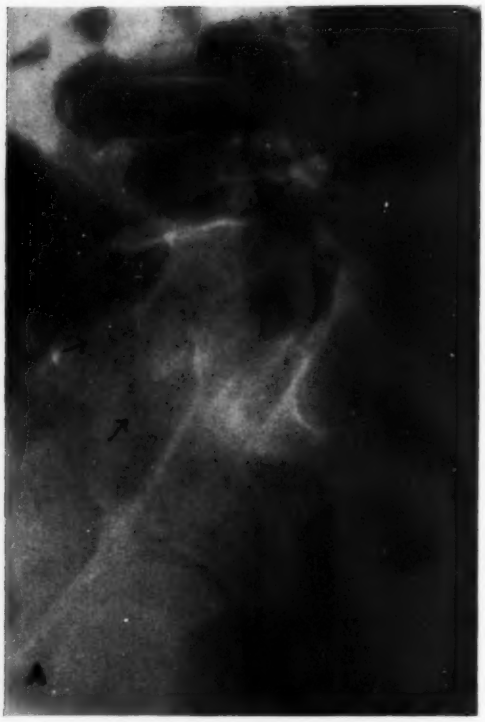


Fig. 1, A. L. L. F. Male, 63. Multiple myeloma (primary focus probably in 5th lumbar body). Destruction of most of body of 5th lumbar vertebra. See also Fig. 1, B and C.

after the diagnosis had been made elsewhere. Other admission diagnoses were: endocarditis; fractured femur; intestinal neoplasm; sternal tumor; sciatica; psychoneurosis; metastatic bone tumor; carcinomatosis of the lumbar spine; pathological fracture; pneumonia; extensive neoplastic or inflammatory process involving the bones.

The chief complaints also varied. Pain was present in 17 of the 18 patients, or 95 per cent. Soft-tissue masses near the sites of the bone tumors were present in 4 cases, or 22 per cent. Significant weight loss occurred in 2 patients, or 11 per cent. Sudden acute pain with pathological fracture was seen in 3 patients, or 16.6 per cent. Paralysis of the lower extremities developed in 2, or 11 per cent. Each of the following complaints was present in 1 case: chest pain; prolonged bleeding from the nose and alveolus (after dental extraction); dizzy spells.

*Laboratory Findings:* Bence-Jones protein was present in 6 of the 18 cases, or 33 per cent; it was present in 36 per cent of the proved cases. Eleven patients had positive bone marrow biopsies. The total serum proteins determined in 14 cases varied from 4.81 gm. per cent to 14.05 gm. per cent, 6 patients having a total protein of 8.0 gm. per cent or over. The blood calcium levels varied from 8.0 mg. per cent to 12.1 mg. per cent, 5 being over 11 mg. per cent. The blood phosphorus levels varied from 3.0 mg. per cent to 4.8 mg. per cent.

*X-ray Findings:* The bones involved, in order of frequency, were the skull (9 cases); ribs (9 cases); femora (7 cases); pelvis (6 cases); clavicles (6 cases); cervical, thoracic, and lumbar spine (5 cases each); scapulae (4 cases); humeri (4 cases). Multiple bony involvement was, of course, present in every instance.

One case well exemplifies the interesting manifestations of this disease and will be mentioned here since it does not fall into our irradiated group (described elsewhere in this article, under Case Reports).

L. L. F., a white male, aged 63, was admitted to the hospital complaining of pain in the left knee and low back for four months. X-ray examination revealed no evidence of disease in the knee; the body of the fifth lumbar vertebra was partly destroyed. Skull films disclosed a circular area of rarefaction in the right parietal bone about 3 cm. in diameter. The other bones and the lungs showed no lesions. *Note:* The ribs and pelvis were radiologically negative. The diagnosis was probable metastatic neoplasm. See Fig. 1, A and B.

*Laboratory Data:* Hemoglobin 58 per cent (8.59 gm.); white blood count 7,050; serum calcium 11.2 mg. per cent; phosphorus 4.0 mg. per cent; blood protein, total 7.2 gm. per cent (albumin 4.2 gm., globulin 3.0 gm.); alkaline phosphatase 1.5 units (rising to 18.8 units six weeks after admission); icterus index (four weeks after admission) 22 units. The urine was negative for Bence-Jones protein. The sternal bone marrow contained 27 per cent abnormal plasma cells.

The biopsy report on a soft-tissue mass over the skull defect was as follows: "Sections reveal a rather edematous, fibrous stroma, throughout which there is a diffuse infiltration with plasma cells. These exhibit the usual polygonal shape with eccentric nuclei and a peripheral arrangement of the masses of chro-

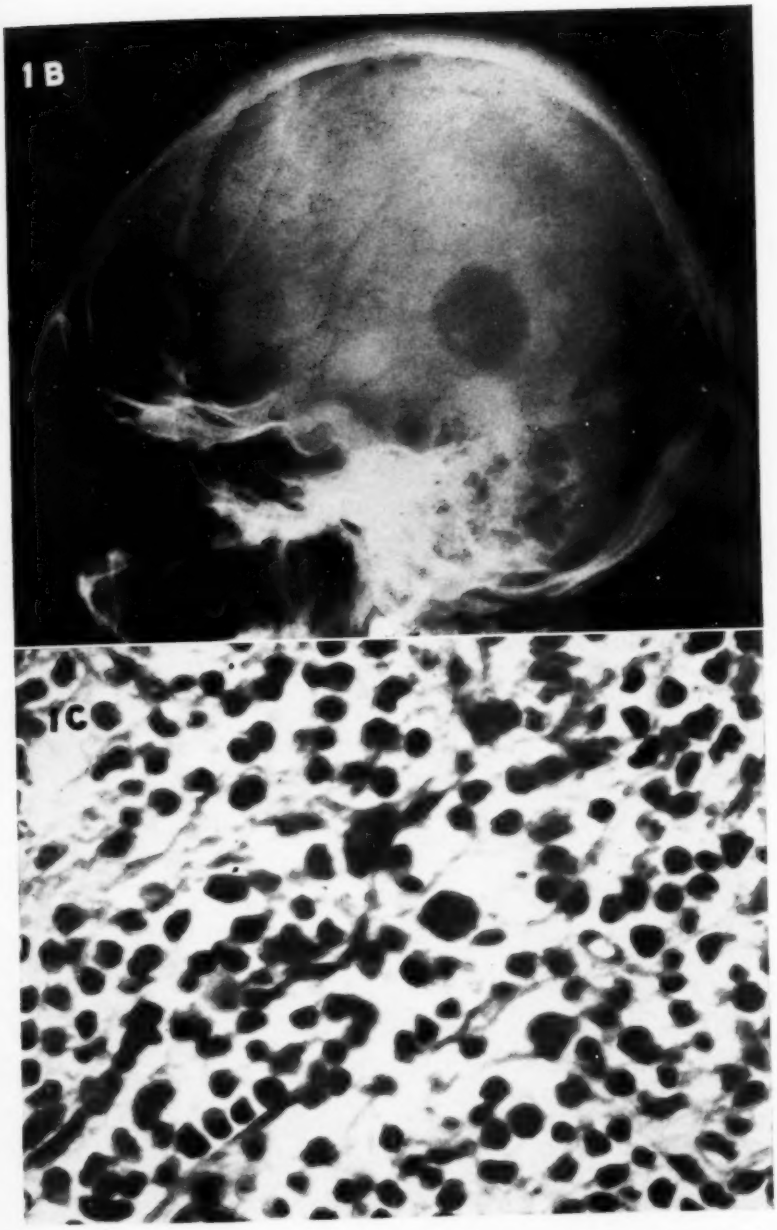



Fig. 1, B and C. Same case as Fig. 1, A. B. Circular area of bone destruction in right parietal bone. The rest of the skeleton was negative. Tentative roentgen diagnosis: Metastatic neoplasm. Biopsy of skull: Plasma-cell myeloma.

C. Tissue from skull biopsy showing a rather edematous, fibrous stroma diffusely infiltrated with plasma cells. These exhibit the usual polygonal shape with eccentric nuclei and a peripheral arrangement of the masses of chromatin. They vary considerably in size, many of them being quite large and a few containing multiple nuclei. *Diagnosis:* Myeloma.

natin. These cells vary considerably in size, many of them being quite large and a few containing multiple nuclei. Several areas of the tissue exhibit hyaline changes, pyknotic nuclei, and necrosis *Diagnosis:* Multiple myeloma." (See Fig. 1, c.)

The patient went rapidly down hill while the tissue just described was under study, and died of cholemia some six weeks after admission.

Autopsy disclosed myelomatous lesions in the lumbar spine and skull, plus a mass in the head of the pancreas, compressing the common bile duct. Microscopically the latter proved to be metastatic myeloma. (Radiation therapy to the upper abdomen possibly *might* have prevented or deferred this fatal outcome by shrinking the pancreatic mass).

*X-ray Treatment:* There were 8 proved cases treated with x-rays. The average duration of life in 7 of these was 10.4 months following irradiation; 1 patient is still living and clinically well nine years after irradiation. Three proved cases were not treated; the average duration of life in these was 2.3 months.

Five patients with microscopically unproved but clinically definite myeloma were irradiated, and their average duration of life was 7.1 months. Two were not treated, and the average duration was 36.3 months!

The physical factors were as follows: 200 kv., h.v.l. 1.2 mm. Cu; target-skin distance and field size varied according to the sites treated (commonly used distances were 70 cm. and fields 20 cm. in diameter). The dose in roentgens was measured in air without back-scatter.

The results of irradiation may be classified as subjective improvement, objective improvement, and no effect. Subjective improvement resulted in 4 patients (relief of pain). Objective improvement occurred in 2 patients, both paraplegics (one regained sensory and motor power; one only sensory). No apparent improvement of any type was found in 7 cases, but in 1 of these irradiation was inadequate (refused by the patient after a single treatment, because of nausea). Partial recalcification of the lesions occurred in 1 case. Therefore, of 13 cases treated, 6 showed improvement, and 7 did not. The details of treatment are listed under the individual case reports and in Table I.

## CASE REPORTS

CASE 1: Mr. G. I., 31-year-old Peruvian, was admitted on Oct. 19, 1929, complaining of difficulty in urination, paralysis of the legs, and severe pains in the back and flanks.

*Laboratory Data:* Hemoglobin 70 per cent (Sahli); red cell count 3,560,000; white cell count 8,550 (polymorphonuclears 82, lymphocytes 16, monocytes 2); blood Wassermann negative; no Bence-Jones protein.

*X-ray examination* of the skull was negative. The cervical, thoracic and lumbar spine, pelvis, and upper femora showed areas of destruction.

*Clinical Diagnosis:* Multiple bone tumors either metastatic from prostate or due to multiple myeloma.

*X-ray Treatment:* 200 r to the lumbar spine.

Patient refused further treatment, and died Nov. 12, 1929.

CASE 2: Mrs. E. O., 59-year-old Irish woman, was admitted on July 16, 1932, with a history of weakness for seven months, swelling of the head for three months, backache and pain in the right thigh for three months. She was emaciated and pale, with a soft, non-tender 8-cm. mass over the left parietal area and another small mass over the mid-occipital region.

*Laboratory Data:* Hemoglobin 54 per cent; red blood cells 3,000,000; total plasma protein 13.0 gm. per cent; no Bence-Jones protein.

*X-ray examination* on July 20 showed a few indefinite areas of rarefaction in the ribs. The lumbar spine was normal except for a questionable area of radiotranslucency in the body of L2. Views of the skull, clavicle, and right femur, on July 27, showed many radiolucent areas.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* 600 r each to the anterior and posterior thorax and pelvis.

No change was noted following therapy. The patient died in six weeks, of bronchopneumonia.

CASE 3: Mr. L. P., a 48-year-old Portuguese, was admitted on Feb. 9, 1934, complaining of continuous alveolar bleeding following a tooth extraction on Jan. 4, 1934; intermittent epistaxis; pain in the right hip and lower lumbar region for four months.

*Laboratory Data:* Hemoglobin 33 per cent; red blood cells 1,700,000; white blood cells 8,600, with a normal differential count and an occasional myeloblast; Bence-Jones protein present.

*X-ray examination* of the skull and ribs was negative; compression of the body of L1 was demonstrated.

*Clinical Diagnosis:* "Endocarditis" and, later, multiple myeloma. The radiology department suggested hyperparathyroidism.

*X-ray Treatment:* 750 r in five days over L1 posteriorly (for pain).

No apparent change followed treatment. Death occurred in one month, due to bronchopneumonia.

TABLE I: CASES OF MULTIPLE MYELOMA TREATED BY X-RAYS

| Case | Sex and Age | Total Dosage (r air)* | Results | Survival |
|---|---|---|---|---|
| 1 | M 31 | 200 r, post., to lumbar spine (inadequate) | Signed release | 0.7 mo. |
| 2 | F 59 | 600 r, ant. and post., to thorax, in 15 days<br>600 r, ant. and post., to pelvis, in 15 days | No change | 1.5 mo. |
| 3 | M 48 | 750 r, post., over L5, in 5 days | No change | 1.0 mo. |
| 4 | M 59 | 1,000 r, post., to thorax, in 10 days | Pain relief | 14.0 mo. |
| 5 | F 51 | October 1939<br>1,000 r, post., to thoracolumbar spine, in 19 days<br>1,000 r, ant., to left hip, in 19 days<br>November 1939<br>400 r, post., to right hip, in 17 days<br>600 r, ant., to right hip, in 17 days<br>100 r, ant., to lumbosacral spine, in 17 days<br>200 r, post., to lumbosacral spine, in 17 days<br>March 1940<br>200 r, ant., to left shoulder, in 18 days<br>200 r, ant., to left hip, in 18 days<br>100 r, post., to left hip, in 18 days<br>100 r, ant., to pelvis, in 18 days<br>100 r, post. to cervical spine in 18 days<br>September 1940<br>600 r, to right neck and skull, in 3 days<br>September 1942<br>1,000 r, ant., to right lower femur, in 6 days<br>1,000 r, to right shoulder, in 6 days<br>100 r, to right frontal bone, in 6 days | Marked subjective improvement | 46.0 mo. |
| 6 | F 35 | 1,200 r, post., to L5, in 15 days<br>800 r, ant., to L5, in 15 days | No change | 1.5 mo. |
| 7 | F 57 | 2,400 r, ant., to thorax, in 30 days<br>700 r, ant., to lumbosacral spine, in 4 days | Pain relief | 12.0 mo. |
| 8 | F 70 | 1,000 r, to right lat. ribs, in 12 days<br>1,000 r, to left lat. ribs, in 12 days<br>1,000 r, to lumbosacral spine, in 7 days | No change | 6.5 mo. |
| 9 | M 36 | 1,000 r, to right clavicle, in 6 days<br>1,000 r, ant., to right pelvis, in 6 days<br>1,000 r, post., to pelvis, in 7 days<br>1,000 r, to right and left lateral skull, in 7 days<br>1,600 r, ant., to right and left shoulder, in 8 days<br>1,300 r, ant., to chest, in 7 days<br>1,400 r, ant., to left hip in 7 days | No change | 6.0 mo. |
| 10 | F 70 | 500 r, ant. and post., to chest, in 15 days<br>2,000 r, ant., to right hip, in 15 days<br>2,000 r, post., to C6, in 15 days | Improvement in pain | 8.5 mo. |
| 11 | M 69 | 2800 r, post., to lumbar spine, in 20 days | Improvement in sensation but not in motor function | 2.5 mo. |
| 12 | F 72 | 550 r, ant., to thorax, in 5 days<br>100 r, post., to thorax in 1 day | No change | 1.5 mo. |
| 13 | M 61 | October 1939<br>1,900 r, ant., over T8 in 1 mo.<br>1,900 r, post., over T8 in 1 mo.<br>July 1941<br>2,100 r, post., over T8 in 10 days<br>October 1941<br>600 r, post., to thorax, in 3 days | Return of sensation and motor function; recalcification of bone; marked improvement | Still living (over 9 yr.) |

* Fields usually large, *e.g.*, 20 cm. diameter; h.v.l. 1.2 mm. copper.

CASE 4: Mr. G. P., 59-year-old Greek, was admitted on July 9, 1936, with a history of pain in the sternum, swelling at the right sternoclavicular junction, and pain in the right subscapular area of twelve months' duration. The patient was thin and in moderate distress; the skin over the manubrium was edematous, red, and tender to pressure.

*Laboratory Data:* Hemoglobin 76 per cent; red blood cells 4,100,000; white blood cells 11,000; total plasma proteins 4.81 gm. per cent; Wassermann reaction negative; Bence-Jones protein present.

*X-ray examination* on July 13 showed radiolucencies of moderate extent in the skull and cervical spine and extensive bone destruction in the sternum.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* 1,000 r in air to the anterior chest, resulting in slight relief of pain.

The patient died fourteen months after admission, from bronchopneumonia and uremia.

CASE 5: Mrs. M. F., 51-year-old white female, was admitted on Oct. 5, 1939, complaining of pain in the right hip, thoracic spine, left lower ribs, and anterior

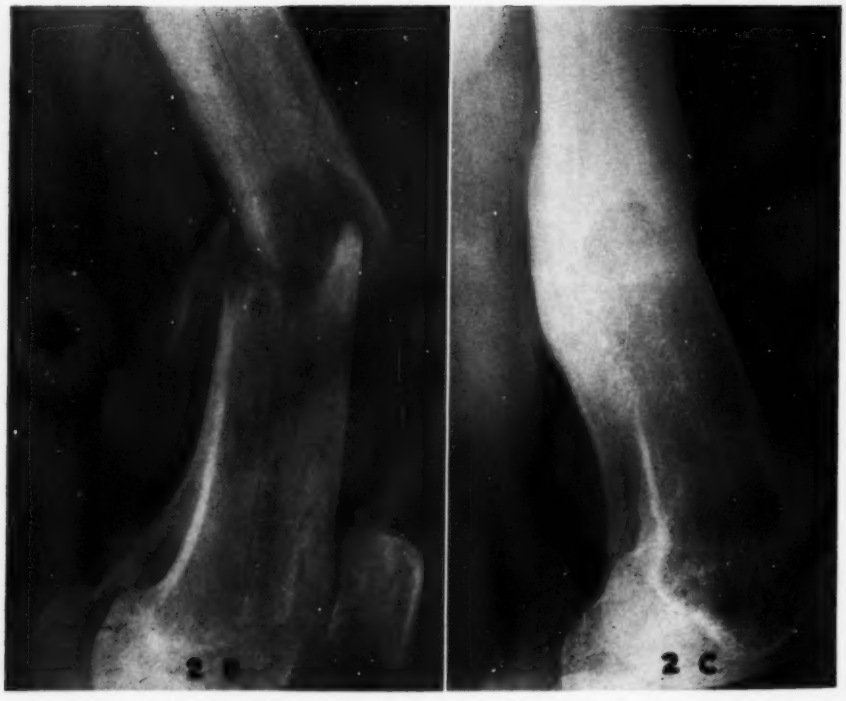
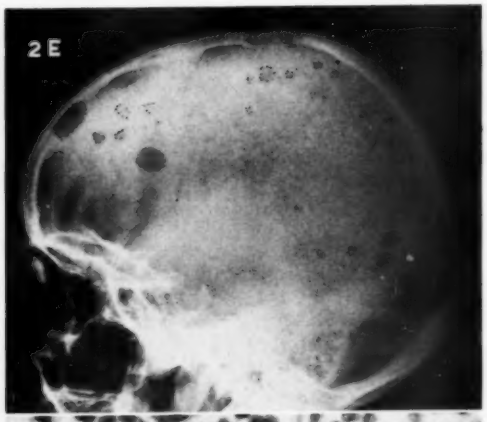



Fig. 2, A, B, C. Case 5: M. F. Female, 51. Multiple myeloma (primary focus not discoverable; multiple lesions when first seen).

A. Destructive lesions in ribs and thoracic spine. Pathological fracture of left 10th rib posteriorly. Biopsy of the rib showed plasma-cell myeloma.

B and C. Pathological fracture, left femur, with healing following irradiation. Remained healed for three and a half years. *Note:* A pathological fracture of the right femur in a similar location occurred approximately two years after the fracture of the left. See also Fig. 2, D–F.



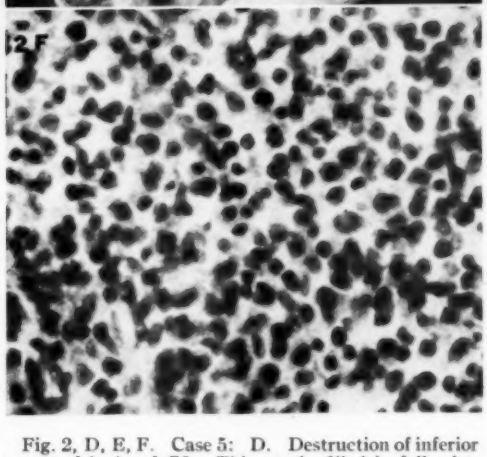




Fig. 2, D, E, F. Case 5: D. Destruction of inferior aspect of body of C2. This partly filled in following irradiation. Pathological fracture of spinous process of C7.

E. Destructive lesions in skull. These regressed partly following irradiation but finally grew in size in the frontal area (some three years after this film).

F. Tissue from rib biopsy showing, scattered through the bone marrow, some large islets of discrete, uniform, rounded, pink cells with dark-staining, eccentrically placed nuclei. Masses of plasma cells have locally crowded out the hemopoietic and myelocytic tissues. *Diagnosis:* Plasma-cell myeloma.

part of the chest for four months. She was a well developed, well nourished woman, lying quietly in bed but having considerable pain on movement.

*Laboratory Data:* Hemoglobin 80 per cent (11.5 gm.); albumin 5.84 gm. per cent and globulin 2.02 gm. per cent; serum calcium 11.1 mg. per cent; phosphorus 3.2 mg.; phosphatase 2.23 units; cholesterol 148 mg. per cent.

A biopsy specimen from a rib was described as follows: Scattered through the bone marrow are some large islets of discrete, uniform, rounded, pink cells with dark-staining, eccentrically placed nuclei. Several of these cells have more than one nucleus, and occasionally there are mitotic figures. There are masses of plasma cells. They have locally crowded out part of the hemopoietic and myelocytic tissues. The surrounding bone marrow shows myeloid and erythropoietic cells in the usual ratio, a moderate number of megalokaryocytes, and a moderate amount of granulation tissue; it is fairly active, however. *Diagnosis:* Plasma-cell myeloma of rib. (See Fig. 2, F.)

*X-ray examination* on Oct. 6, 1939, showed two 2-cm. areas of radiolucency in the left ilium; osteoporosis of the cervical and thoracic spine; radiolucencies in the skull and extensive radiolucent lesions in the ribs. The findings on subsequent examinations were as follows: March 25, 1940: Lumbosacral spine, increase in the rarefaction. Nov. 13, 1940: Pelvis, no change. Nov. 27, 1940: *Left* femur, pathological fracture. March 8, 1941: Skull, no change; sternum negative. April 12, 1941: Healed fracture of the femur. July 18 and 21, 1941: Pathological fracture of the 6th rib and right acromion. July 24, 1941: Skull, enlargement of lesions; humerus, multiple lesions; *right* femur, lesions with pathological fracture; pelvis, no change; hands and feet, negative.

*Clinical Diagnosis:* Extensive neoplastic process involving the bones.

*X-ray Treatment:* The first course in October and November 1939, over a period of nineteen days, consisted of 1,000 r to the posterior thoracolumbar spine and 1,000 r to the left hip anteriorly; second course, latter part of November and first part of December 1939 (17 days), 400 r to right hip posteriorly; 600 r to right hip anteriorly; 100 r anteriorly to the lumbosacral spine, and 200 r to the posterior lumbosacral

spine. Marked subjective improvement followed these courses. A third course, in March 1940 (eighteen days), consisted of 200 r to the left shoulder, 200 r to the left hip anteriorly, 100 r to the left hip posteriorly, 100 r to the pelvis, 100 r to the posterior cervical spine. A fourth course, in September 1940 (three days), consisted of 600 r to the right lateral neck and skull.

In November 1940 the patient was admitted with herpes zoster, and while she was in bed a pathological fracture of the left femur was noted. This was treated with a hip spica. She was discharged and observed periodically, but no further treatment was given, until September 1942, following occurrence of a pathological fracture of the right femur. A dose of 1,000 r was then given to the lower anterior right femoral area in six days; then 1,000 r to the right shoulder anteriorly in six days; then 1,000 r to the right frontal bone in six days. A phagedenic ulcer developed about a traction pin in the tibia in November 1942, and death occurred on March 6, 1943, of acute purulent meningitis. Survival of *46 months*.

CASE 6: Mrs. M. D., 35-year-old Irish female, was admitted on Feb. 25, 1941, with back pain and left sciatica of four months' duration. She had been seen in one of the University Out-Patient clinics for several weeks before entry, with a diagnosis of psychoneurosis.

*Laboratory Data:* Hemoglobin 94 per cent; red blood cells 5,050,000; total serum proteins 6.9 gm. per cent; serum calcium 9.6 mg. per cent; serum phosphorus 4.3 mg. per cent; phosphatase 6.7 units; Bence-Jones protein present.

A sternal marrow biopsy showed plasma-cell myeloma.

*X-ray examination* on Feb. 28, 1941, showed extensive areas of radiolucency in the skull, ribs, pelvis, and the body of L5.

*Clinical Diagnosis:* A diagnosis of multiple myeloma was made one week after admission. Provisional diagnoses were numerous: sciatica, peripheral neuritis, herniated nucleus pulposus, compression fracture, hysteria, cancer phobia, pelvic inflammatory disease, etc.

*X-ray Treatment:* 1,200 r to a 20-cm. field centered over L5 posteriorly and 800 r anteriorly in fifteen days.

The patient died on May 3, 1941, having survived 1.5 months after diagnosis. Death was due to bronchopneumonia.

CASE 7: Mrs. M. K., 57-year-old Negro female, was admitted on March 1, 1940, complaining of progressive pain in the back for many months and recent radiation of the pain down the right leg; also, swelling over the sternum for fourteen months. The patient was a thin, elderly appearing woman in considerable pain. A 6-cm. mass was present in the supramanubrial area, with heavy pigmentation of the overlying and adjacent skin.

*Laboratory Data:* Hemoglobin 54 per cent; red blood cells 2,950,000; white blood cells 3,950, with a normal differential count; total blood proteins 14.05 gm. per cent (albumin 3.27 gm.; globulin 10.78 gm.); no Bence-Jones protein.

*X-ray findings* were as follows: March 1, 1940: Sternum, osteolytic tumor of the manubrium sterni, most probably "chondroma or giant cell." March 6, 1940: Shoulder and elbow, negative. April 20, 1940: Skull, osteolytic lesions; pelvis, negative; lumbar spine, negative; thoracic spine, irregular decrease in density in T8. April 23, 1941: Chest, thoracic spine, and skull, no change. Aug. 15, 1941: Chest, negative; skull, no change; cervical spine and pelvis, negative. Dec. 11, 1941: Thoracolumbar spine, no change.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* Between March 7 and 11, 1940, the patient received 1,200 r to the upper sternum; this was repeated in twenty days. There was some relief of pain and decrease in size of tumor. Nine months later she received 700 r to the lumbosacral spine anteriorly. Death occurred Dec. 4, 1942, of bronchopneumonia.

CASE 8: Mrs. B. V., 70-year-old Swiss female, was admitted on Sept. 22, 1944, with back and flank pain of nine weeks' duration. The patient had sustained a pathological fracture of the left clavicle one year earlier, which was treated by irradiation. The diagnosis at that time was "chondroma"! Physical examination revealed pain on movement and a 5-cm. mass over the acromial end of the left clavicle.

*Laboratory Data:* Hemoglobin 79 per cent; red blood cells 3,600,000; white blood cells 7,800, with normal differential count; total blood proteins 11.4 gm. per cent (albumin 2.89 gm.; globulin 8.6 gm.); serum calcium 10 mg. per cent; phosphorus 3.0 mg. per cent; no Bence-Jones protein.

Sternal biopsy showed plasma-cell myeloma.

*Roentgen findings* were as follows: Sept. 29, 1944: Fracture of the 8th and 9th ribs; T10 and T11 wedge-shaped (myelomatous at necropsy). Oct. 4, 1944: Pelvis, including the upper femora and lower lumbar spine, multiple radiolucencies varying from 2 to 3 mm. in diameter; similar lesions in ribs, scapula, cervical spine, and clavicles. Oct. 10, 1944: Skull, multiple radiolucent areas up to 1 cm. in diameter. Jan. 9, 1945: Marked progression of the lesions in the pelvis, thoracolumbar spine, and ribs, the last showing multiple fractures.

*Admission Clinical Diagnosis:* Bone tumor, possibly multiple myeloma, with pathological fractures.

*X-ray Treatment:* 1,000 r each to the right and left sides of the thorax in twelve days; 1,000 r to the lumbosacral spine in seven days.

There was no marked improvement, and the patient died on March 29, 1945, of bronchopneumonia. Necropsy confirmed the diagnosis of multiple myeloma.

CASE 9: Mr. J. O., a 36-year-old white male, was admitted on Dec. 23, 1944, having broken a leg, slipping on a curb.

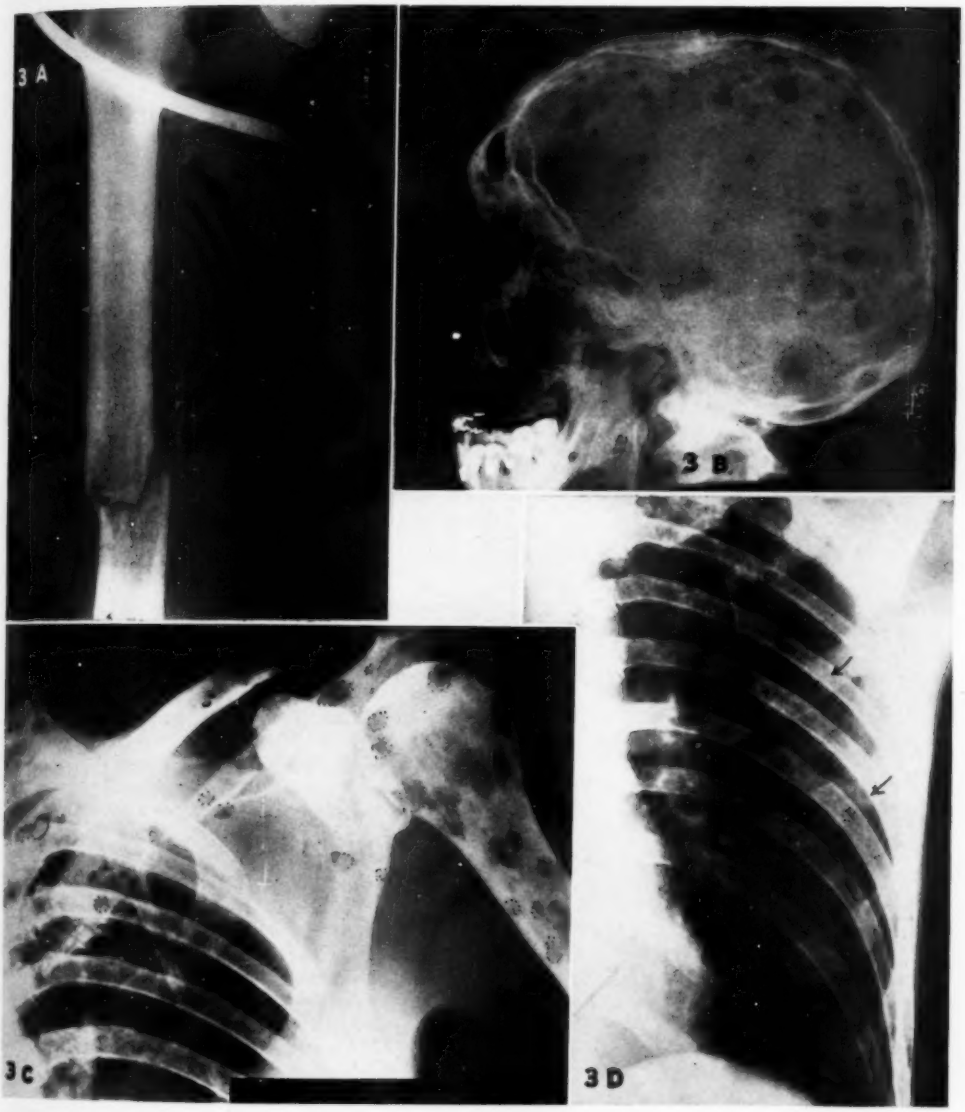



Fig. 3. Case 9: J. O. Male, 36. Multiple myeloma (primary focus apparently in femur, "metastasizing" after four months).

A. Pathological fracture, shaft of right femur. Film made six days after entry; admission film showed minimal destruction; present film shows extensive bone destruction about fracture site (first apparent focus in this case).

B. Skull, five months after admission. "Typical" myelomatous lesions. Films at admission were negative.

C. Left shoulder, 6 months after admission. Multiple destructive lesions in clavicle, scapula, humerus, and ribs.

D. Ribs, six months after admission. Multiple lesions. Six weeks previously rib films were negative.

*Laboratory Data:* Hemoglobin 76 per cent; red blood cells 3,700,000; white blood cells 13,800, with normal differential count; total blood proteins 6.7 gm. per cent (albumin 3.2 gm.; globulin 3.5 gm.); serum calcium 11.3 mg. per cent; phosphorus 4.8 mg. per cent; no Bence-Jones protein.

A biopsy specimen from the right femur revealed plasma-cell myeloma.

*Roentgen examination* on Dec. 23, 1944, showed a pathological fracture of the shaft of the right femur in good position. Films of the skull (Jan. 4, 1945) were negative.

Frozen section of the leg lesion on Jan 27 showed "undifferentiated malignant tumor," and a subtrochanteric amputation was done. Further *x-ray findings* were as follows: April 9, 1945: Chest, clear; pelvis, areas of decalcification in the right pubic bone, stump of the femur, and both ilia. April 14, 1945: Skull, many radiolucencies, ranging from 2 to 20 mm. in diameter. April 20, 1945: Multiple radiolucencies in clavicles, scapulae, humeri, and ribs.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* 1,000 r to the right shoulder anteriorly in six days; 1,000 r to the right pelvis anteriorly in six days; 1,000 r to the posterior pelvis in seven days; 1,000 r to the right and left lateral skull in seven days; 1,600 r to the right and left shoulder in eight days; 1,300 r to the chest anteriorly in seven days; 1,400 r to the left hip anteriorly in seven days.

Treatment was followed by a decrease in pain in the shoulders, left hip, pelvis, and chest. Death occurred on June 21, 1945, from uremia.

CASE 10: Mrs. C. S., a 70-year-old Irish female, was admitted on July 24, 1945, because of chronic nausea and anorexia, 60-pound weight loss in eight months, and chest pain for six months.

*Laboratory Data:* Hemoglobin 54 per cent; red blood cells 2,700,000; white blood cells 5,360, with normal differential count; total blood proteins 7.2 gm. per cent (albumin 2.7 gm.; globulin 4.5 gm.); Wassermann reaction negative; no Bence-Jones protein.

A sternal marrow biopsy showed plasma-cell myeloma.

*X-ray Findings:* July 25, 1945: Chest, multiple areas of rarefaction in the right clavicle, left scapula, humerus, and ribs, with a fracture of the right 7th rib. Aug. 2, 1945: Skull, multiple radiolucencies; lumbar spine, negative. Oct. 24, 1945: Radiolucencies in the femora, lumbar spine, and pelvis, with a fracture of the pubic bone. Nov. 21, 1945: Pelvis, no change. Dec. 13, 1945: Cervical spine and mandible, multiple lesions. March 13, 1946: Pathological fracture of the left humerus.

*X-ray Treatment:* 2,000 r to the right hip anteriorly in fifteen days; 500 r each to the anterior and posterior thoracic area in fifteen days; 200 r to the posterior cervical region in fifteen days.

Some relief of pain followed. Death, due to bronchopneumonia, occurred March 18, 1946.

CASE 11: Mr. L. R., 69-year-old white male, was admitted on Nov. 7, 1946, complaining of sudden pain in the back while stooping over a wash basin, causing him to fall to the floor. Physical examination showed paralysis of both legs, bladder, and bowel, and sensory loss up to the mid-thigh.

*Laboratory Data:* Hemoglobin 11.8 gm. (74 per cent); red blood cells 3,780,000; white blood cells 8,500 (polymorphonuclears 58, lymphocytes 40, basophils 2); Wassermann reaction negative; total blood proteins 7.6 gm. per cent (albumin 5.9 gm.; globulin 1.7 gm.); serum calcium 8 mg. per cent; phosphorus 4.7 mg. per cent; alkaline phosphatase 5.5 Bodansky units; Bence-Jones protein present on one occasion.

Sternal biopsy revealed plasma-cell myeloma.

*X-ray Findings:* Skull negative. Pathological fracture of several ribs. Some destruction of T12 and L2.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* 2,800 r to the spine in approximately three weeks, followed by some improvement in sensation only.

Death ensued Dec. 28, 1946, from anemia and cachexia.

CASE 12. Mrs. K. G., 72-year-old white female, was admitted on July 17, 1941, complaining of "rheumatic" pains in both shoulders, radiating to the hands, for eighteen months.

*Laboratory Data:* Hemoglobin 23 per cent; red blood cells 1,200,000; white blood cells 9,500; Wassermann reaction negative; 70 per cent Bence-Jones protein in urine; blood urea nitrogen 156 mg. per cent. Sternal biopsy showed 50 per cent plasma cells. Subsequent laboratory findings were: hemoglobin 59 per cent (10 gm.); red blood cells 4,200,000; white blood cells 4,600 (polymorphonuclears 78 per cent, lymphocytes 18 per cent, myelocytes 4 per cent). In one month the red cell count dropped to 1,070,000 and the hemoglobin to 17 per cent. Serum protein 8 gm. per cent; calcium 10 mg.; phosphatase 3.4 units.

*X-ray Examination:* Skull, chest and pelvis, negative.

*Clinical Diagnosis:* Multiple myeloma.

*X-ray Treatment:* 550 r to the anterior chest and clavicles in five days; then 100 r posteriorly.

Pain was not relieved and death occurred Aug. 21, 1941, from cardiac failure.

CASE 13: Mr. J. P., 61-year-old white male, was first admitted to the medical service of the San Francisco Hospital on May 14, 1939, with chills, fever, and chest pains of two weeks' duration. Physical examination revealed dyspnea, generalized chest pain, dullness over the right upper lobe anteriorly and posteriorly, blood pressure 110/80, temperature 103.6°. X-ray examination on the day of admission showed consolidation in the lower portion of the right upper lobe, presumably lobar pneumonia.

Neufeld examination of the sputum for pneumococci was negative. Blood culture after one week showed no growth but later (twelve days after admission) yielded an unidentified gram-negative rod. The blood Wassermann reaction was negative. The hemoglobin was 80 per cent; red blood cells, 4,000,000; white cells 16,000. The urine showed albumin (type unspecified).

The clinical diagnosis was lobar pneumonia. The course was complicated by a pleural effusion and a lung abscess. On July 13, 1939, the patient was discharged as improved.

On Sept. 30, 1939, the patient was re-admitted, complaining of abdominal pain and postprandial

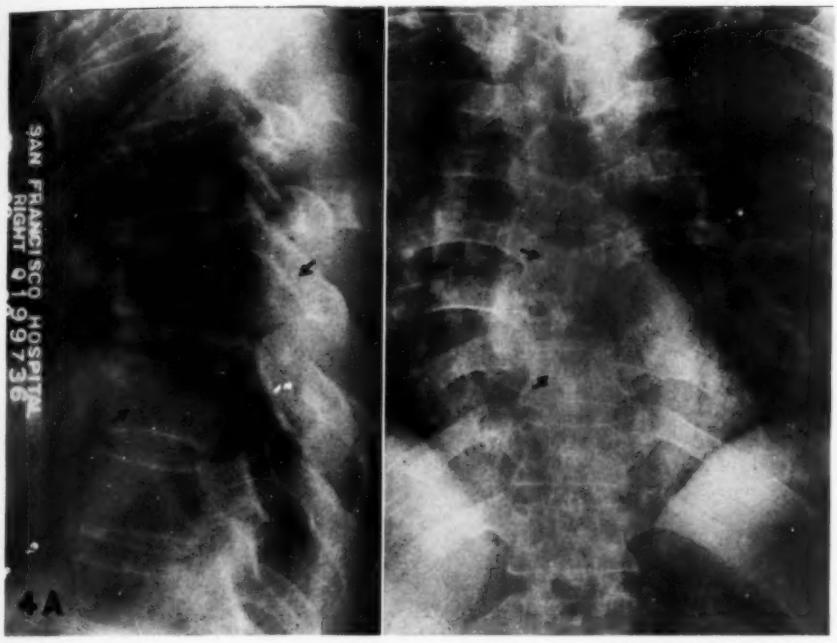



Fig. 4. A, Case 13: J. P. Male, 61. Multiple myeloma. Destruction of body of T8 and expansile lesion of adjacent left 8th rib (1939). See also Fig. 4, B–G.

distention for three months; a feeling of numbness over the abdomen and legs, and stiffness of the legs for one month; inability to walk and bladder difficulty for five days.

The positive neurological findings at this time were: (1) flaccid paralysis of both legs, except for slight ability to flex the thighs on the trunk, (2) knee and ankle jerks equal and hyperactive, (3) ankle clonus on the right, (4) positive bilateral Babinski sign, (5) cremasteric and abdominal reflexes absent, (6) absence of pain sense up to T8, (7) diminution of vibratory sense in the legs, (8) lower extremity touch sense intact, (9) distention of the bladder, (10) palpable spinal kyphos with crepitation in the region of the 7th and 8th thoracic vertebrae.

*Laboratory Data:* Blood Wassermann negative; urine negative for Bence-Jones protein; red blood cells 4,700,000; hemoglobin 85 per cent; white blood cells 8,100 (polymorphonuclears 61, lymphocytes 38, eosinophils 1); serum proteins 8.65 gm. per cent (albumin 3.88 gm.; globulin 4.77 gm.); blood phosphorus 3.2 mg. per cent. A lumbar puncture revealed an initial pressure of 140 mm. water. Jugular compression reproduced pain in the legs but no rise in pressure. Pandy 2 plus. Lange 0012333211.

*Clinical Diagnosis:* Incomplete transverse myelitis at the level of T8.

*X-ray examination,* in October 1939, showed a destructive lesion with compression of body of T8 and a large expansile lesion in the adjacent posterior third of the left 8th rib. The skull was negative.

Fig. 4 B. Case 13 seven years after Fig. 4, A, showing some recalcification in the lesions involving T8 and left 8th rib (not well shown in this reproduction). New lesions present in other thoracic bodies and ribs. See also Fig. 4, C–G.

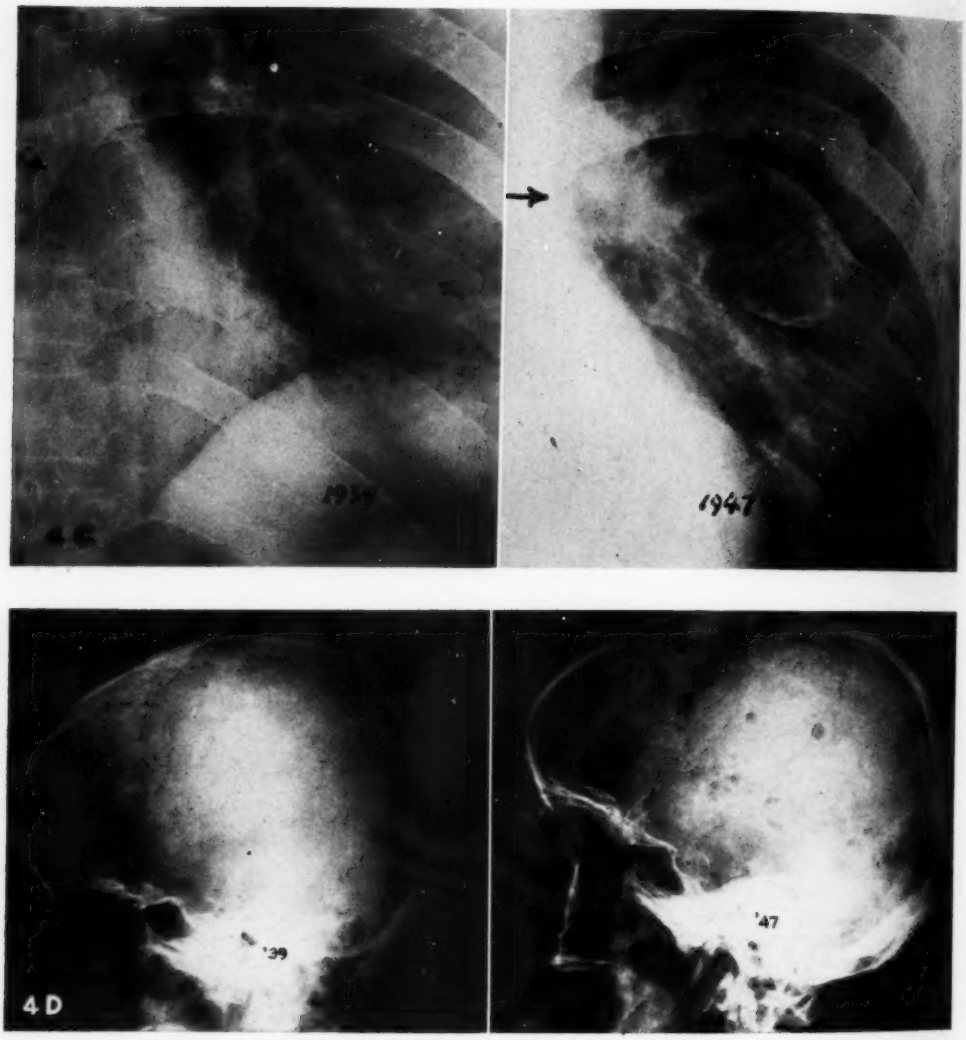



Fig. 4, C and D. Case 13: C. Left 8th rib before treatment and again eight years later, showing partial recalcification. Also healed fracture of left 7th rib.
D. Skull in 1939 and 1947, showing development of myelomatous foci.

The pelvis and right femur showed several small areas of decreased density.

The patient was placed in a posterior shell cast. On Oct. 21, 1939, a rib biopsy was performed by Dr. Halter, and grossly the lesion appeared to be a sarcoma or myeloma. Considerable bleeding was encountered during the procedure. The pathological report was as follows: The section shows a dense mass of cells scattered uniformly throughout a scanty, relatively vascular stroma. No bone or normal marrow is seen. The majority of the individual cells have moderately large, oval to round, dark nuclei with fine chromatin network and very scanty pink cytoplasm. There is a moderate variation in size and shape of the cells. There are no true plasma cells but occasional cells with dark, round, eccentrically placed nuclei. Some cells contain two large nuclei. *Diagnosis:* Myeloma, rib (myeloblastic type). (See Fig. 4 F.)

On Oct. 25, 1939, deep roentgen therapy was begun. In approximately thirty days 1,900 r (in air) were given to the anterior and 1,900 r to the posterior thorax, over a circular field 20 cm. in diameter (distance 70 cm.; h.v.l. 1.2 Cu) centered over T8.

On Nov. 12, 1939, the patient was able to wiggle the toes of both feet, slightly dorsiflex the feet, flex

Fig. 4, E. Case 13. Pelvis in 1947, showing multiple foci.

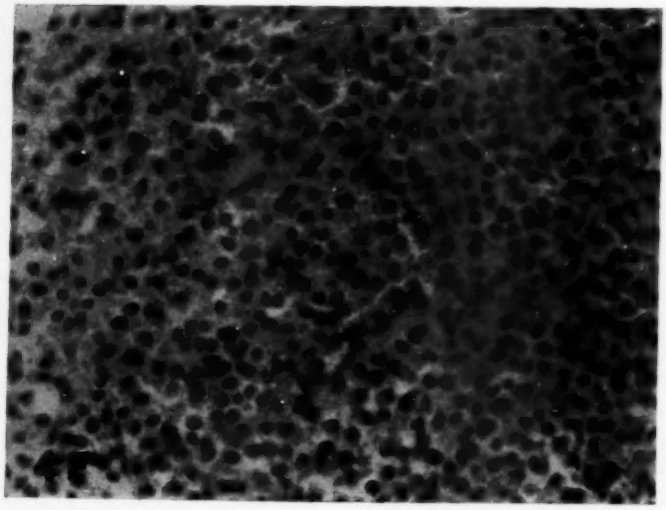


Fig. 4, F. Case 13: Tissue from rib showing numerous cells, a majority of which have moderately large, oval to round, dark nuclei with a fine chromatin network and very scanty pink cytoplasm. There is a moderate variation in size and shape of the cells. There are no typical plasma cells, but occasional ones with dark, round, eccentrically placed nuclei; some contain two large nuclei. Diagnosis: Myeloma, rib (myeloblastic type).

the right knee, abduct the right leg at the hip, and move both legs slightly in extension from a flexed position. He gradually improved and was discharged on Jan. 3, 1940.

X-ray examinations in November and December 1939 showed apparent progression of the left 8th rib lesion and development of new areas of rib destruction elsewhere. The spine showed no change.

The patient dropped from sight and was recorded in our files as probably dead. On June 30, 1941, he

Fig. 4, G. Case 13. Patient in October 1947, eight and a half years after treatment for multiple myeloma with paraplegia. Clinically well.

came in, walking, complaining of stiffness in the left foot and pain in the back. Films showed further compression of T8. The margins of T7 and T9 were now involved. The large lesion in the left 8th rib showed partial bone regeneration. A second course of radiation was given: 2,100 r (in air) in ten days to the posterior thorax centered over T8, with the same factors as before.

By August 1941, the patient was walking and looking better. He gained four pounds by Oct. 2, 1941. During the latter part of October, however, he hurt his back trying to lift a man! X-ray examination revealed some molding of T12, but no change in T8. The posterior thoracic area was given 600 r in three days, with the same factors as previously.

On Nov. 14, 1941, a plaster cast was applied to the lower thorax and abdomen. The urine at this time was still negative for Bence-Jones protein.

On Jan. 12, 1942, the pain had practically disappeared and the patient was anxious to have the cast removed; this was done the following day and films of the spine showed more compression of T12 than had been apparent on Oct. 30, 1941. There was some recalcification of the body of T8 and of the left 8th rib.

The patient was discharged and followed at short intervals in the Outpatient Department. In March he remarked "If I were just a little stronger, I would get a job in the shipyards." In May 1942 he was seen again and was doing well. He had hurt his left chest two weeks earlier, jumping over a creek(!), but continued to do well except for another attack of pneumonia in July 1942. In February and June 1943, films of the cervical spine were negative; the thoracic spine showed no significant change.

The patient was not seen again until March 18 1944; he felt well and additional irradiation therapy was not considered to be necessary at the moment. The skin over the treated area on the back was slightly telangiectatic and atrophic; anteriorly it was pale but showed no other changes. X-ray examination in December 1946 showed skull involvement for the first time. New radiolucent areas had developed in the spine and ribs.

In January and again in November 1947, the patient reported in response to follow-up letters, looking and feeling well. He had been working as a night watchman. Laboratory examination in January revealed: hemoglobin 82 per cent (14.0 gm.); red blood cells 4,200,000; white cells 8,000 (polymorphonuclears 64, lymphocytes 25, eosinophils 2, myelocytes 7). The urine was negative for albumin, sugar, acetone, and Bence-Jones protein. Films of the skull, spine, ribs, pelvis, and upper femora revealed many new radiolucencies. The spinal and rib lesions in the irradiated area were partly recalcified. The blood calcium was 9.4 mg. per cent; phosphorus 3.0 mg. per cent, total protein 8.35 gm. per cent; (albumin 3.58 gm.; globulin 4.77 gm.).

## DISCUSSION

The consensus of opinion in the general radiological literature is that "multiple myeloma is a radiosensitive lesion." Most authors stop with that statement and cite no really convincing evidence with which to support it.

In addition to the authors to whom reference has been made (Shields Warren, 28; Ackerman and del Regato, 1; Pohle, 21), Leucutia, and several other radiation therapists (3, 10, 19) have displayed rather optimistic attitudes toward the radiation responsiveness of this disease. However, in a recent refresher course summary (Am. J. Roentgenol. **58:** 247, 1947) we note that Leucutia has expressed a more cautious attitude, as follows: "Radiation therapy leads to *limited* symptomatic relief, but no cure is possible."

Ehrlich (10) comes close to our own attitude when he writes: "X-ray treatment aids the clinical symptom of bone pain when present, and may temporarily retard the progressive bone destruction. Prognosis is still very poor."

One might expect some correlation between irradiation dosage and results. The more adequate dosage (up to reasonable limits, say 2,500 tissue roentgens tumor

TABLE II: SUMMARY OF RESULTS OF ROENTGEN TREATMENT

| Case | Microscopic Findings (Type of Myeloma) | Maximum Tissue Dosage to Any One Lesion (Calculated to Middle of Principal Tumor in Area Treated) | Results and Duration of Life After Diagnosis | |
|---|---|---|---|---|
| 1 | ... | 200 r in 1 day to lumbar spine | None (inadequate dosage) | 0.7 mo. |
| 2 | ... | 1,000 r in 15 days to thorax and pelvis | No change | 6 wk. |
| 3 | ... | 700 r in 5 days to L5 | No change | 4 wk. |
| 4 | ... | 830 r in 10 days to posterior thorax | Pain relief | 14.0 mo. |
| 5 | Plasma-cell | 1,000 r in 19 days to lower thoracic and upper lumbar spine | Marked subjective improvement | 46.0 mo. |
| 6 | Plasma-cell | 1,660 r in 15 days to L5 | No change | 1.5 mo. |
| 7 | ... | 1,992 r in 11 days to anterior thorax | Pain relief | 12.0 mo. |
| 8 | Plasma-cell | 1,000 r in 4 days to the lumbosacral spine | No change | 6.5 mo. |
| 9 | Plasma-cell | 1,892 r in 8 days to the shoulders | No change | 6.0 mo. |
| 10 | Plasma-cell | 2,240 r in 15 days to C6 | Pain relief | 8.5 mo. |
| 11 | Plasma-cell | 2,800 r in 20 days to lumbar spine | Improvement in sensation | 2.5 mo. |
| 12 | Plasma-cell | 540 r in 15 days to thorax | No change | 1.5 mo. |
| 13 | Myeloblastic | 2,660 r in 30 days to T8 | Return of sensation and motor function; recalcification of bone; marked improvement | Still living, over 9 yr |

dose in a period of two to four weeks) might be expected to give improved results. A review of the literature and study of our own dosage-result tabulation (Table II) suggests that such is not the case. Some authors maintain a preference for moderate dosage (200 r × 3 in one week); others would give radiation to tolerance (200 r × 20 to each area). The answer to this problem is not yet available. "Solitary" myelomas appear to merit intensive treatment; multiple myelomas with spinal cord compression probably benefit from fairly heavy dosage (*e. g.*, Case 13, above); multiple myelomas with pain over the involved flat bones or extremities may often be handled fairly well with moderate dosage (*e. g.*, Case 5, above).

## SUMMARY

The authors review the results of x-ray treatment of multiple myeloma as reported in the literature, and in a series of 13 cases treated at the San Francisco Hospital. Six of these cases showed improvement; 6 were not appreciably benefited; 1 had incomplete treatment.

One of the patients survived over nine years and is still living; he is ambulatory and in good clinical condition, despite an initial grave paraplegia. The average survival for the remaining proved x-ray-treated cases was 10.4 months, while that of the untreated cases was only 2.3 months.

These results are distinctly inferior to those of Batts (3), who reported a survival period of 23 months in a roentgen-irradiated group and 6.0 months in an untreated group. This difference may be due to variation in the stage of the disease in the two groups, plus variation in the roentgen dosage in some of the authors' cases.

It is believed that adequate irradiation of patients with multiple myeloma is still worth attempting, though the results will unquestionably disappoint those who accept commonly published statements that these lesions are "very radiosensitive."

## CONCLUSIONS

*Multiple* myeloma is not a very radiosensitive disease. The average duration of life after diagnosis was 10.4 months in all but one of the authors' treated cases. In this latter case there was a survival of over nine years and the patient is still living, exemplifying the good result one may occasionally obtain in the treatment of this disease.

"*Solitary*" myeloma appears to be a radiosensitive and radio-controllable disease in certain instances, and should be treated by vigorous roentgen irradiation when the diagnosis is established microscopically.

*Multiple or "solitary"* myeloma with spinal cord compression and paresis or paraplegia appears to be well worth irradiation (following laminectomy). In the

literature, survivals for as long as seven years have been recorded. The authors' patient who survived nine years was in this group. He is clinically well, though with extensive roentgenographic evidence of myelomatosis.

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## DISCUSSION

**Grantley W. Taylor, M.D.** (Boston, Mass.): I feel flattered to be invited to discuss Dr. Garland's paper, although I do not pose in any way as an authority in myeloma. I have followed these cases for many years at Huntington Hospital and Massachusetts General Hospital and I confess, after a long period of observation, to being completely confused as to myelomas.

I am glad Dr. Garland expressed a note of caution and I am entirely in agreement with him that these tumors are not especially sensitive to radiation. Our own experience has led us to a good deal of pessimism. Irradiation is the only effective medium of therapy in myeloma that we have and therefore we use it, but we do not often see very satisfactory or very brilliant results. It may be that the cell type, to which attention has been drawn, is of a good deal of significance. It is interesting that Dr. Garland's one case with so long a survival and so striking a reaction to treatment proved to be of a type other than the usual plasma-cell myeloma.

The stilbamidine which we hailed with so much enthusiasm a year or so ago has washed out for us pretty much. We do not feel that it does enough good to warrant pursuing its use to a very considerable extent.

Dr. Garland perforce, because of the brevity of the time, had to pass over some of the things which were included in his paper, to which I will just refer. One is the laboratory aids to diagnosis. Bence-Jones protein, in our experience, as in his, is a rare and freakish type of finding. When it is present it is of some help, although it is not pathognomonic; in most of the cases it seems to be absent or you have to make frequent observations to discover it. The level of protein is of much more significance and we find, as did he, that in almost all cases there is a considerable elevation of total protein and a reversal or a change in the albumin-globulin ratio.

The difficulty is that in myeloma we are dealing with a process we do not well understand, our standards for the life history of the disease are not well established and not standardized. and in many cases

there are not true spontaneous remissions and regressions, but merely spontaneous episodes of a sense of well-being in the patient only to be followed by an apparent retrograde activity in the disease. I think the more observations that can be made on the variations in the natural history of this disease and on the correlation of these variations with the cell type, the better off we may be.


SUMARIO

**Roentgenoterapia del Mieloma Múltiple**

Los AA. repasan el resultado obtenido por la roentgenoterapia en el mieloma múltiple, tal como aparece en la literatura y en una serie de 13 casos tratados en el Hospital de San Francisco. De estos últimos casos, 6 mostraron mejoría, 6 no se beneficiaron apreciablemente, y en 1, el tratamiento fué incompleto.

Uno de los enfermos todavía vive, al cabo de más de nueve años; puede andar y se halla en buen estado clínico, a pesar de una grave paraplejía inicial. La sobrevivencia media para los demás casos reconocidamente tratados con los rayos X fué de 10.4 meses, comparado con no más de 2.3 meses para los casos no tratados.

Este resultado es decididamente inferior al conseguido por Batts, quien comunicó un período de sobrevivencia de 23 meses en un grupo irradiado con rayos X y de 6.0 meses en otro no tratado. Esta diferencia puede deberse a hallarse la enfermedad en distintos períodos en los dos grupos, y además a variación en la dosis roentgenológica en algunos de los casos de los AA.

Parece que todavía vale la pena probar la irradiación adecuada en el mieloma múltiple, aunque los resultados decepcionarán sin duda a los que aceptan los asertos corrientes de que dichas lesiones son "muy radiosensibles." En el mieloma múltiple o solitario con compresión de la médula espinal y parálisis o paraplejía, en particular parece que vale la pena ensayar la irradiación (consecutivamente a la laminectomía). En este grupo se han comunicado en la literatura sobrevivencias hasta de siete años, y la sobrevivencia prolongada descrita en la serie de los AA. fué en un caso de este género. El mieloma solitario parece ser radiosensible y radiocoercible en ciertos casos y debe ser tratado con la irradiación enérgica, una vez establecido microscópicamente el diagnóstico.

# Histologic Changes in Squamous-Cell Carcinoma of the Mouth and Oropharynx Produced by Fractionated External Roentgen Irradiation[1]

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MOST HISTOLOGIC studies of irradiation changes have been based on the effect of a single massive radium exposure producing overwhelming destructive changes in the tumor. Few histologic studies have been made of the effects of fractionated roentgen irradiation, although this method predominates in modern radiotherapeutic technics. The administration of roentgen rays in small daily fractions permits the normal epithelium to recover somewhat each day from the irradiation injury, while the less differentiated tumor cells, for the most part, show no evidence of recovery. Fractionation also increases the number of times each tumor cell is exposed to irradiation while in the premitotic or mitotic phase, which is believed by many to be the most radiosensitive phase.

Melnick and Bachem (1) described the findings in transplantable tumors of rats following both the single massive dose method and fractionated, protracted irradiation. With the massive dose method, they noted radiation necrosis of tumor cells, associated with hyperemia, cellular infiltration, granulation tissue proliferation, fibrosis, and blood vessel changes. With the fractionated protracted technic they observed, in addition to necrosis of radiosensitive cells, a gradual transformation of all the refractory tumor cells into hyperchromatic giant cells. These cells did not degenerate by necrosis, but by calcification of the nucleus. This method of treatment had no apparent effect on the adjacent normal tissues. There was no fibrosis and no blood vessel damage.

Halley and Melnick (2) described the changes observed in twenty-one breasts that were irradiated preoperatively. Their findings were similar to those observed in animal tumors.

Glücksmann (3) studied the effects on human squamous-cell and basal-cell carcinoma of different technics of fractionated roentgen and gamma-ray irradiation with varying daily and total doses. He evaluated in each biopsy specimen the dividing, degenerating, resting, and differentiating cells. The dividing cells showed rapid and early reduction of the number of mitotic figures, which often reached zero in eighty minutes. Later there was partial resumption of mitotic activity, chiefly in the form of abnormal mitoses. Many of these "broke down," contributing to the "degenerating cell" count, that increased until mitotic activity ceased. In successfully treated carcinoma, mitotic division ultimately ceased. Reduction of the number of resting cells in the growing areas of the tumor was due either to degeneration or differentiation. Increased differentiation of the cells in most cases was related to a fall in the resting cell count. Glücksmann (3) regarded many of the monster-sized cells as differentiating cells; this is contrary to our impression. He concluded that the aims of treatment were: to cause disappearance of the malignant dividing cell; produce a high degenerate cell count; reduce the number of

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non-dividing resting cells; and to increase the number of differentiating cells at the expense of the resting cells. In summary, he stated that the success of irradiation is best evaluated by comparing the number and character of young cells surviving at stated intervals after irradiation.

The purposes of this study are (1) to describe and evaluate the histologic changes occurring in irradiated squamous-cell carcinoma of the mouth and oropharynx; (2) to describe certain other attendant phenomena, such as radiation keratogenesis and the mechanism of formation of the various types of giant-sized tumor cells; (3) to illustrate schematically the probable mechanism of radiation degeneration of radiosensitive, moderately radiosensitive, and radioresistant squamous-cell carcinoma; (4) to study the effect of irradiation on the stroma; (5) to study the effect of inadequate irradiation.

## MATERIALS AND METHODS

The material studied was obtained from 28 patients with squamous-cell carcinoma of the mouth and oropharynx, who were subjected to periodic biopsies during treatment. The 28 cases are grouped according to anatomic location and clinical radiosensitivity as shown in Table I.

### *Irradiation Procedures*

Beginning in 1932, a carefully controlled group of patients with carcinoma of the upper respiratory tract was treated with a standard irradiation technic at Bellevue Hospital. The reactions of the tumor, skin, and mucosa to this irradiation have been recorded in graphic form (Figs. 1 and 2) and analyzed (4, 5). From this series, 28 lesions in which serial biopsies were performed constitute the basis for this study.

In the administration of fractionated external irradiation with high-voltage roentgen rays (200 kv., 0.5 to 2.0 mm. copper filter), the two most important factors are the size of the daily tumor dose and the number of days over which the treatment is given. With this in mind, two technics were employed: a standard technic capable of destroying a carcinoma; a substandard technic entailing one-half of the daily dose of the standard technic. The total dose was the same with both methods.

TABLE I: CLASSIFICATION OF TUMORS ACCORDING TO SITE AND RADIOSENSITIVITY*

| Location | Radiosensitive | Radioresistant |
|---|---|---|
| Soft palate | 1 | 1 |
| Floor of mouth | 5 | 1 |
| Retromolar | 1 | 3 |
| Tonsil | 4 | 2 |
| Antrum | 1 | 0 |
| Tonsillar pillar | 2 | 3 |
| Alvelar ridge | 0 | 1 |
| Tongue | 0 | 3 |

* Radiosensitive tumors are those that apparently disappeared completely after external irradiation. Radioresistant tumors are those that failed to disappear completely after external irradiation.

Because of the irregular configuration of the mouth, jaw, and neck, any attempt to indicate the actual daily dose delivered into the tumor is an approximation. The average total skin dose delivered in twenty-five to twenty-eight days was 4,000 r (measured with back-scatter) to each of two lateral neck portals. The physical factors were: 200 kv., 0.5 mm. or 2.0 mm. copper filter; 20 ma.; 50 cm. target-skin distance; 10 × 15 cm. portal, with an occasional 8 × 10 cm. portal; half-value layer of 0.9 or 1.8 mm. copper; dosage rate from 10 r/min. to 40 r/min., the most common being 30 r/min.

1. *Standard Treatment Technic:* The standard technic consisted in the administration of a daily skin dose of 400 r (with back-scatter), given either in the form of 200 r to the right and to the left sides of the neck each day, or 400 r daily to one alternate neck portal. This provided an approximate *average daily tumor dose of 275 r.* The beams of radiation were aimed so as to cross-fire the tumor. Treatments were given five or six days a week. The total tumor dose averaged approximately 6,000 r to 6,500 r in twenty-three to twenty-eight days. Twenty-four patients were thus treated.

A typical case is illustrated in Figure 1. The patient had a carcinoma of the

tonsillar pillar. He was treated through two lateral neck portals, 8 × 10 cm. each, and received a daily skin dose of 390 r (measured with scattering) to one alternate portal. A total skin dose of 3,900 r was delivered to each of the two portals. This was delivered in twenty treatments over a period of twenty-five days. There resulted a third-degree reaction or epithelitis (thin curved line) in the mucosa, that healed by the forty-ninth day, and a second-degree reaction or epidermitis in the skin (heavy curved line), that healed by the fortieth day. In order to destroy a radiosensitive squamous-cell carcinoma of the upper respiratory tract, it is usually necessary to produce at least a second-degree epithelitis and epidermitis. These reactions of the skin and mucosa are an indication of the amount of destruction produced by radiation and serve as a guide in the treatment of a patient. Since many biopsy specimens of irradiated tissue contain normal epithelium as well as tumor cells, the changes in these can be compared.

The broken line in Figure 1 represents the shrinkage of the tumor. This curve is based on clinical observations and, though subject to errors in interpretation, has prognostic value. The radiosensitivity and radiocurability of a tumor are proportional to its rate of shrinkage. For example, if the tumor has shrunk approximately 50 per cent in size by the sixteenth to the eighteenth day, there is a strong likelihood that it will be completely destroyed by the standard course of x-ray therapy. If the rate of shrinkage is slower, roentgen therapy will have to be supplemented with other forms of treatment.

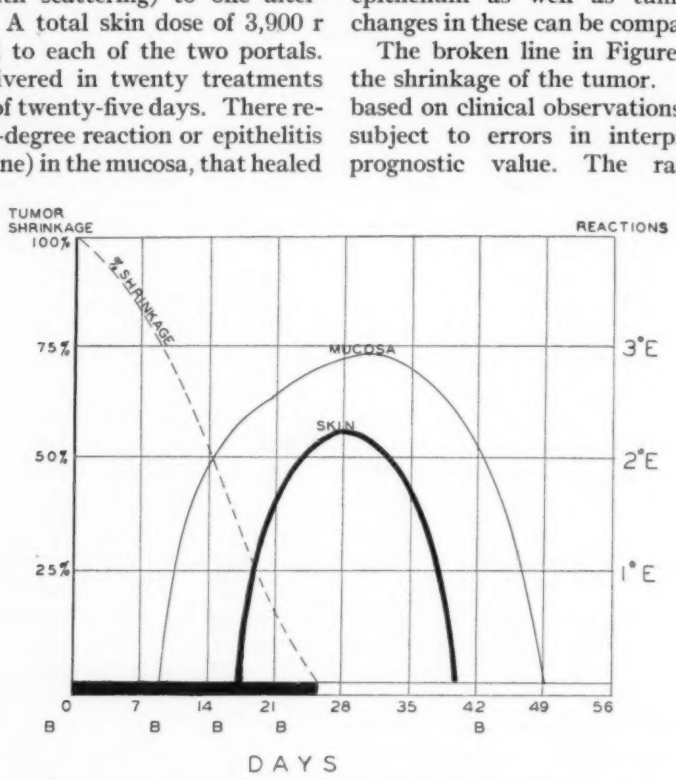


Fig. 1. Graph illustrating tumor shrinkage and reactions of skin and mucosa in a typical case of carcinoma of the tonsil receiving standard irradiation. The factors were: 200 kv.; 20 ma.; 50 cm. distance; 8 × 10 cm. portal; 0.5 mm. copper and 1 mm. aluminum filter; h.v.l. 1.0 mm. Cu; dosage rate 30 r/m. The daily skin dose was 390 r (measured with scattering) to one alternate lateral face portal; total dose, 3,900 r to each of two lateral face portals; approximate average daily tumor dose, 275 r; total tumor dose, 5,500 r in twenty-three days.

There was a mild second-degree epidermitis, and a severe second-degree epithelitis (in the region where biopsies were taken). The tumor was radiosensitive and disappeared completely on the twenty-seventh day. B (at bottom of graph) indicates day of biopsy.

2. *One-half Standard Treatment Technic* (Fig. 2). The "one-half standard treatment technic" consisted in the administration of a total daily skin dose of one-half of the standard amount, namely 200 r (measured with scattering). This was either given in the form of 100 r to the right and left side of the neck each day, or 200 r daily to alternate portals. The average daily tumor dose was approximately 135 r. In order to achieve the same total dose as with the standard technic, the daily treatments were extended over approximately twice the length of time. One patient was treated for fifty-six days (Fig. 2). The others were irradiated over a period of fifty-one, sixty-seven, and one hundred and four days, respectively.

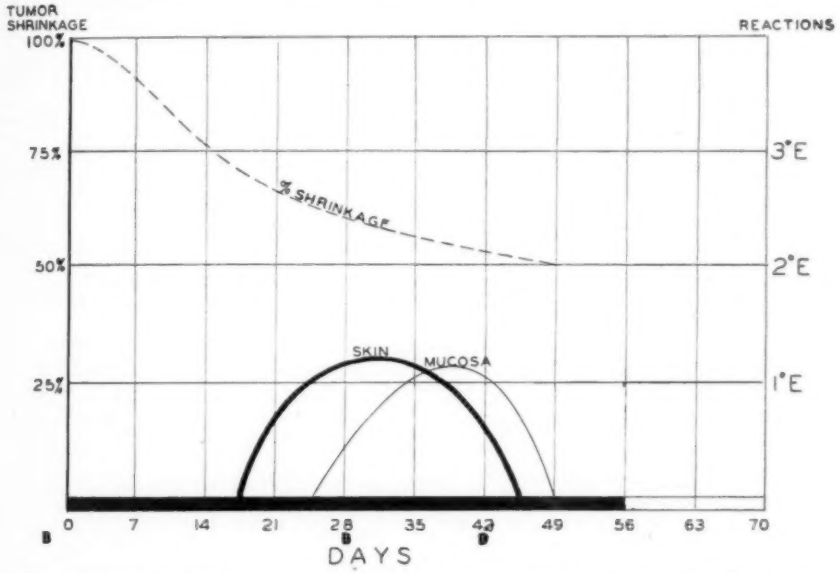


Fig. 2. Graph illustrating tumor shrinkage and reactions of skin and mucosa of a radioresistant, under-irradiated tumor, receiving one-half the standard daily dose. The daily tumor dose was 135 r and the total tumor dose was 5,400 r in fifty-five days. Reactions of skin and mucosa healed during treatment due to active recovery processes during the healing phase. The tumor shrank 50 per cent and recurred several months later. B (at bottom of graph) indicates day of biopsy. See Figure 14.

The "one-half standard technic" was an experimental technic, using an inadequate daily dose for the purpose of eliciting and clarifying certain recovery responses following irradiation. It was used in 4 cases. Figure 2 illustrates the reaction curves of a typical case. The patient had a carcinoma of the tonsil with metastases in the regional lymph nodes. Treatment was given through two lateral neck portals measuring 10 × 15 cm., the daily dose being 100 r (measured with scattering) to each portal, for a total daily dose of 200 r. The total skin dose was 4,080 r to each of the two portals. This was delivered in 40 treatments over a period of fifty-six days.

The administration of each daily destructive dose of radiation evokes a companion recovery effect. Successive doses of radiation become cumulative in their effect. It has been shown (5) that recovery effects are also cumulative. A large daily dose of radiation depresses recovery processes and permits only a small recovery effect. As can be seen in Figure 2, the small total daily dose of 200 r has permitted a strong recovery effect, resulting in a tardy onset and mild intensity of skin and mucosal reactions. Furthermore, the strong recovery process

that attends inadequate daily irradiation is reflected in complete disappearance of the reactions while irradiation is being given, and only partial shrinkage of the tumor, which, under standard treatment, probably would have shrunken completely.

This capacity to recover during the course of prolonged irradiation was observed not only in normal stratified squamous epithelium, but also in certain tumors. If the destructive effect of irradiation on a tumor is sublethal, the tumor will again grow even during irradiation.

TABLE II: TIME DISTRIBUTION OF 140 BIOPSIES

| | |
|---|---|
| Before irradiation | 27 |
| Weeks after beginning irradiation | |
| 1/2 | 5 |
| 1 | 9 |
| 1 1/2 | 11 |
| 2 | 11 |
| 3 | 20 |
| 4 | 17 |
| 5 | 9 |
| 6 | 10 |
| 7 | 8 |
| 8 | 3 |
| 9 | 2 |
| 10 | 3 |
| 11 | 0 |
| 12 | 1 |
| 13 | 1 |
| 14 | 1 |
| 20 | 1 |
| 22 | 1 |

### *Biopsy Material*

The biopsy material (Table II) consisted of 140 specimens from 28 patients. The number of biopsy specimens in each case varied from three to nine, with an average of five. Each patient had a pre-treatment biopsy, with the exception of one whose earliest biopsy specimen was taken twenty-four hours after the first treatment. In the beginning of the study, biopsy specimens were routinely taken at weekly intervals over a period of thirty-five to forty-two days. It was soon observed that many important changes occurred during the first two weeks, and consequently additional specimens were taken in this period. In a few cases biopsy specimens were obtained four, eight, twelve, and twenty-four hours after the first treatment. After the twenty-eighth day, when the average course of treatment was concluded, the histologic changes occurred at a slower rate and the interval between biopsies was thereafter increased to two or more weeks. For the purpose of studying late fibrosis, healing changes, and recurrences, biopsy specimens from 17 patients were taken between the fortieth and one hundred and fifty-first day.

The usual criticism of a study of this type is that a particular biopsy specimen may not be representative of the histologic structure of the tumor. Therefore, the number of pieces of tissue removed each time varied from one to four, with an average of two, from different areas of the tumor. Each piece was larger than the usual biopsy specimen, varying from 5 × 6 mm. to 9 × 12 mm., with an average of 6 × 8 mm. When a tumor involved more than one anatomic structure (*i.e.*, tonsillar pillar and tongue), specimens were obtained from each area. Whenever possible, an attempt was made to remove a portion of the adjacent normal epithelium for study. During the first two weeks, when the tumor was bulky, a biopsy punch was used and numerous pieces of tissue were obtained from various areas. After the fourteenth day, the tumor would become flat and fibrous, so that a wedge of tissue would be excised with a scalpel under novocain anesthesia. Bleeding was usually readily controlled with pressure. These multiple biopsy procedures did not seem to influence the rate of growth or spread of the tumor.

*Fixatives and Stains:* The majority of the biopsies were fixed in 10 per cent formalin; a few in Zenker's fluid. Hematoxylin and eosin stains were routinely employed. The following special stains were used: alum hematoxylin to demonstrate keratohyalin, picro-nigrosin to demonstrate eleidin, and Mallory's phosphotungstic acid hematoxylin to demonstrate epithelial prickles and fibrils in the epidermis. Connective tissue was studied with Masson's trichrome stain. Von Kossa's silver nitrate method was used to demonstrate calcification of keratin and tumor cells.

## OBSERVATIONS

The histologic changes produced in tumor cells following irradiation of squamous-cell carcinoma are of the following major types:

1. Acute cell death.
2. Progressive enlargement to giant-sized tumor cells.
3. Radiation keratogenesis.

A tumor undergoing destruction by irradiation usually shows various combinations of the changes enumerated above, although one or even two of these changes may predominate in a single tumor. Each type of change has special therapeutic and prognostic significance.

### *Acute Cell Death*

Acute cell death is the most common radiation effect observed in radiosensitive cells. Its importance has been overlooked because cells undergoing this change rapidly disappear from the tissues and are not seen in later biopsy specimens. Furthermore, the observer's attention is diverted by the bizarre changes occurring in the remaining cells.

The process of acute cell death is chiefly lysis of the nucleus and cytoplasm. Some pyknosis and karyorrhexis occur, but to a slight extent. The cells undergoing acute cell death swell little, if at all. The cell, including cell membrane, nucleus, cytoplasm and mitotic figures, rapidly disappears from view.

Acute cell death occurs chiefly during the first week of irradiation. In a radiosensitive tumor (Fig. 3, A), acute cell death may commence twenty-four to forty-eight hours after the first treatment and proceed so rapidly that, by the seventh day, 50 per cent or more of the tumor cells may have disappeared (Fig. 3 B). Occasionally, a few less sensitive cells undergo acute cell death at a slightly slower rate and persist through the second week. In this event, while lysis is still the dominant feature observed, karyorrhexis and pyknosis become more prominent (Fig. 3, C).

Some radiosensitive cells are unaffected by irradiation for several weeks, or show only slight swelling and vacuolation. When they finally succumb to radiation, they may degenerate in a manner similar to that seen in acute cell death. Such cells, undergoing *delayed cell death*, are proportionately small in number (Fig. 15, D). Occasionally a massive dose of radiation delivered to a radioresistant tumor may produce acute cell death.

Following lysis and disappearance of tumor cells, there remain for a brief time adult connective-tissue fibers with wide interstices, formerly occupied by the tumor cells (Fig. 15, B).

### *Giant-sized Tumor Cells*

Another characteristic cell change produced by irradiation is the progressive and striking enlargement of the tumor cells, some of which attain a giant size. In order to facilitate study of this process, we have arbitrarily designated as "giant-sized tumor cells" those whose diameter is greater than 60 microns. Although these large cells were counted and used as an index, nevertheless similar changes of lesser degree occurred in smaller cells.

As stated previously, the most radiosensitive cells usually undergo acute cell death. The remaining, less radiosensitive cells undergo progressive enlargement and in some instances reach a giant size. A small dose of radiation delivered to a radiosensitive tumor may cause a mild destructive effect resulting in progressive enlargement to giant-sized tumor cells.

In the present study, the roentgen dose remained constant, but the varying susceptibility of the cell determined whether the mechanism of degeneration was to be acute cell death or the formation of giant-sized cells. Melnick (1) used a tumor of constant radiosensitivity and varied the dose. With a dose of 20 S.E.D. (10,500 r), he obtained acute necrosis in two to three days; with 6 to 8 S.E.D. (3675 r) necrosis occurred after a latent period of five days; however, with a small dose, 3.8 S.E.D. (2000 r), there resulted mutation-like

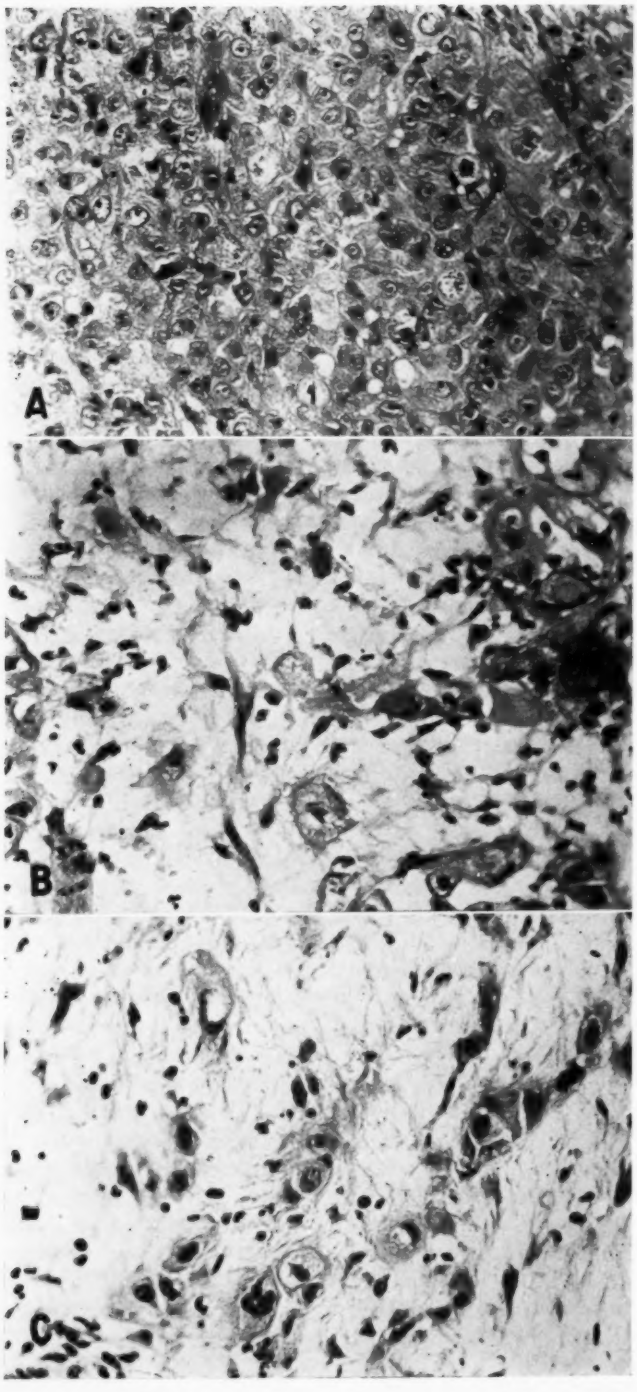


Fig. 3. Undifferentiated squamous-cell carcinoma of soft palate, radiosensitive.

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pleomorphism ending in complete degeneration in fourteen to sixteen days (giant-sized tumor cells).

Tumors showing pleomorphism (including large-sized cells) in the biopsy specimen taken before treatment have a greater tendency toward giant-sized tumor cell formation following irradiation than do tumors showing little or no pre-treatment pleomorphism. Thus an inherent tendency of a tumor cell toward pleomorphism may be accentuated by irradiation.

In the biopsy specimens studied, giant-sized tumor cells began to appear in the latter part of the first week. They increased in number, becoming most numerous toward the end of the second week and the beginning of the third week of treatment, and usually disappeared completely near the end of the seventh week (see Fig. 5, A, B, and C).

Whenever the tumor recurred, as it did in 5 cases in our series, it usually resembled the original tumor and was devoid of any giant-sized tumor cells. This suggests that most giant-sized tumor cells are mutation forms incapable of survival or reproduction. In two recurrent tumors there was a slight increase in pleomorphism; this might be attributed to a permanent non-lethal translocation of chromosomes with resultant viable mutants. However, it is equally plausible that the increased pleomorphism resulted from alteration of the tumor bed, vascular supply, rate of growth, and other factors known to influence the appearance of tumor cells. The material studied does not solve this question.

There are two different types of giant-sized tumor cells: those showing swelling and vacuolation (physical-chemical changes) and those showing nuclear aberrations (chromosome derangements).

*Type 1. Swelling and Vacuolation Due to Physical-Chemical Changes:* Giant-sized tumor cells showing physical-chemical changes present such varied appearances as to warrant a description of each component part of the cell—cell membrane, nuclear membrane, and the nuclear material.

The appearance of the cell membrane may be influenced in three ways. It may be accentuated by marked vacuolation of the cytoplasm, by condensation of the adjacent cytoplasm, or by the formation of a perimeter of keratin in the cytoplasm. As the cell progressively enlarges, the cell membrane finally ruptures and the cytoplasmic content streams out into the surrounding tissues (Fig. 4, B).

Concerning the cytoplasmic alterations in giant-sized tumor cells, there are two types of change: diffuse, expansile swelling of the cytoplasm and formation of degenerative vacuoles. In diffuse expansile swelling, the cytoplasm increases in volume and stains palely, as though it had been diluted with fluid (Fig. 5, B and C). This process usually becomes complicated by the simultaneous formation of vacuoles, although not infrequently a cell may reach giant size without having any vacuoles. At the same time, the nucleus may enlarge in a similar fashion. It is not unusual, however, to see marked cytoplasmic swelling with either a normal-sized or only a slightly enlarged nucleus.

Failla (6) has offered an explanation of the mechanism of cytoplasmic swelling. The permeability of the cell or nuclear membrane is altered, with consequent increased rate of osmosis. During irradiation, there occurs an increased dispersion of electrolytic ions both in the cells and in the fluid of the surrounding spaces. The extracellular ions are carried away by the tissue fluids, leaving a relatively increased concentration of ions within the cell. In order to re-establish equilibrium, the cell absorbs fluids, thereby becoming markedly swollen.

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A. Appearance before treatment. ×*c*.275

B. Biopsy taken on 7th day. Lysis of most of the tumor cells has occurred, leaving "cell spaces." The remaining cells reveal different stages of lysis. ×*c*.275

C. Biopsy on 14th day. A less radiosensitive area showing delayed acute cell death. Lysis of tumor cells is less marked. ×*c*.275

The formation of vacuoles probably occurs through a physical-chemical process similar to that of diffuse swelling. The size and number of vacuoles vary considerably in different tumors and in different cells of the same tumor. Vacuole formation is nevertheless a progressive process. It starts either in a few cells with a few small vacuoles that increase in size and number, or else with minute vacuoles in the perinuclear region (Fig. 5, B). There may be one or a few large clear vacuoles in the cytoplasm (Figure 4, B and 5, C), or a moderate number of similar-sized vacuoles evenly distributed throughout the entire cytoplasm. Numerous vacuoles may almost completely replace the cytoplasmic material and compress the remnants into thin, axial strands that radiate from the nucleus to the cell membrane. A single cell may show successive stages wherein small vacuoles coalesce to form large vacuoles of various sizes.

The appearance of some cells suggests that diffuse swelling and vacuolation are different stages of a single process. Of the physical-chemical changes, vacuolation is the most frequent. In a few of the tumors, however, diffuse swelling of the cytoplasm is the dominant process.

Vacuolation also occurs in the nucleus, but at a later date and to a lesser extent than in the cytoplasm. On occasion, vacuolation may be marked in the cytoplasm but absent in the nucleus. Under these circumstances, there is usually some other type of alteration present in the nucleus as described below.

*Type 2. Nuclear Aberrations Due to Chromosome Derangements:* Irradiation produces a greater variety of degenerative forms in the nucleus than in the cytoplasm. In those tumors that exhibit pronounced nuclear alterations as a result of irradiation, biopsy specimens taken between the seventh and twenty-first days will show progressive stages in the development of abnormal nuclear forms.

Frequently when the "before" specimen shows variation in size and shape of the nucleus, and hyperchromatism, these nuclear alterations are likely to be accelerated and intensified by subsequent irradiation (Fig. 5). It is not uncommon, in islands of tumor cells having a central core of keratinized cells and a peripheral band of prekeratinized polyhedral cells to find that during the course of irradiation the central core will undergo progressive keratogenesis, whereas the peripheral cells will undergo progressive nuclear alterations.

In the nucleus undergoing hyperchromatism, the following more or less progressive changes are observed (Fig. 5): an increase in the number of small chromatin granules; large masses of chromatin irregularly distributed throughout the nucleus; swollen nucleoli, taking a deep esosinophilic stain; varying degrees of condensation of the chromatin so that finally there results a large hyperchromatic nucleus of variable shape; vacuolation of the large hyperchromatic nuclei, the vacuoles varying considerably in size and number. Eventually, in the third and fourth weeks, there are karyorrhexis and karyolysis of the large hyperchromatic nuclei.

In the enlarging nuclei that are becoming hypochromatic, the following more or less progressive changes are to be observed: focal condensation of chromatin material into small granules resulting in vesiculated nuclei; transformation of chromatin into globules of palely staining material; vacuolation of the large hyperchromatic nuclei; chromatin evenly distributed throughout the nucleus in the form of palely staining fine powdery granules; and finally various degrees and stages of karyolysis. In the later stages, after the third week, there may be seen an occasional isolated large, pale nuclear shadow in the connective-tissue stroma. This may represent late karyolysis of a disrupted hypochromatic or a previously hyperchromatic nucleus.

The above descriptions apply to giant-sized tumor cells. However, in cells that enlarge slightly, the changes observed are the same except that they are generally milder in degree and represent an earlier stage of degeneration. These cells may be

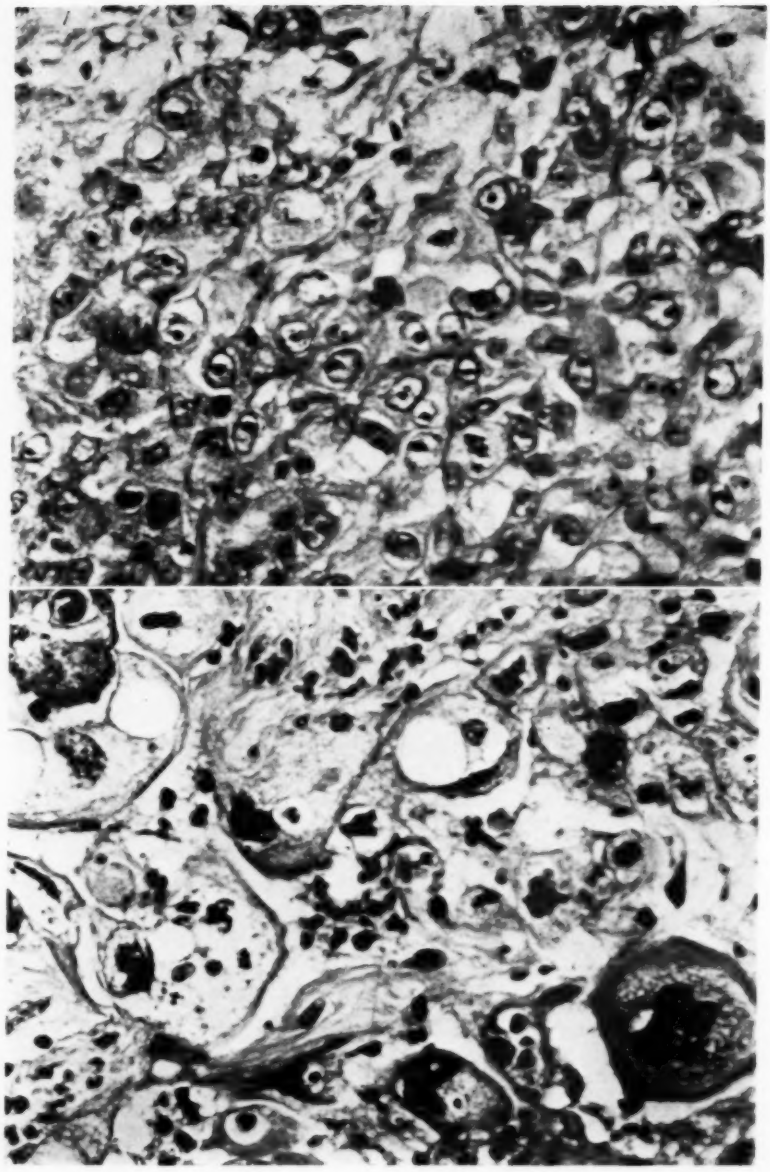

Fig. 4. Undifferentiated squamous-cell carcinoma of soft palate, moderately radiosensitive.

A. Appearance before treatment. ×500

B. Biopsy on 21st day of treatment. Giant-sized tumor cell formation due predominantly to swelling and vacuolation of the cytoplasm. Cell in lower right hand corner reveals perinuclear fine vacuolation of the cytoplasm; around the periphery is a zone of early keratinization. Elsewhere are seen various stages of cytoplasmic swelling and vacuolation, with one cell bursting and its contents streaming into the tissue. ×500

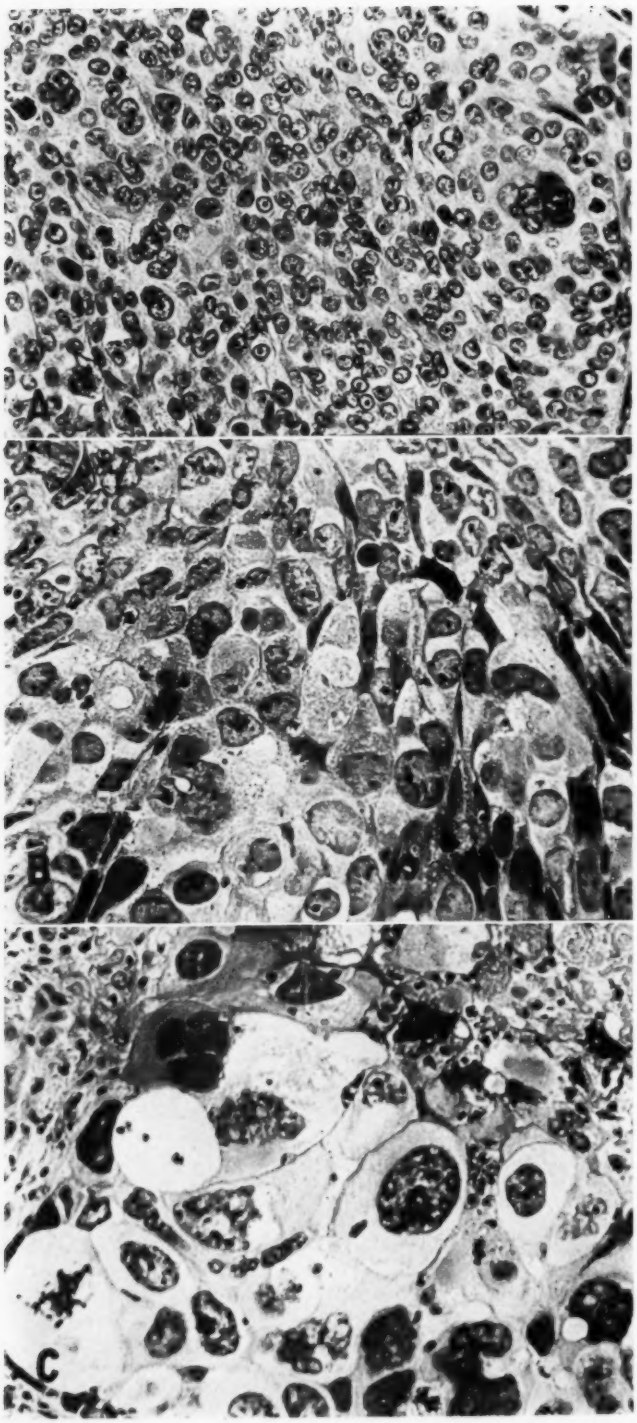


Fig. 5. Undifferentiated squamous-cell carcinoma of floor of mouth.
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present in the same specimen together with giant-sized tumor cells (Fig. 5). Occasionally, these smaller cells may show advanced degenerative changes such as karyolysis. This is the type of change more often seen in acute and delayed cell death.

In a radioresistant tumor, the degenerative changes may be slight in degree, delayed in time of appearance, or absent.

*Mitotic Figures:* Mitotic figures were studied by counting separately the normal and abnormal figures in fifteen representative high-power fields in each biopsy specimen. Three average counts were obtained for each specimen: one for normal mitotic figures, one for abnormal, and one for the total number of mitotic figures. These were plotted in a graph (Fig. 6). In the group of abnormal mitotic figures there were included only those bizarre forms produced by radiation injury. The atypical mitotic figures commonly found in untreated tumors were considered to be normal for the tumor and were therefore grouped with the normal mitotic figures.

Examination of Figure 6 indicates that the number of normal mitotic figures, averaging 1.6 per high-power field, drops precipitously during the first fourteen days. By the end of this period, normal mitotic figures have almost completely disappeared, except in an occasional radioresistant tumor that may contain a few normal mitotic figures as late as seven weeks after the first treatment. In contrast, abnormal mitotic figures, that were rare in the unirradiated specimen, increased in number rapidly during the first week. During the second week they decreased in number so that by the fourteenth day few were present. In some radioresistant tumors, a few abnormal mitotic figures were observed as late as six weeks after the beginning of treatment.

There is a probable relationship between radiation-induced abnormal mitoses and giant-sized tumor cells due to nuclear aberrations. The latter are the end-result of the process of cell division disturbed by irradiation. In Figure 7, the average incidence of abnormal mitotic figures is compared with that of giant-sized tumor cells. As stated above, abnormal mitotic figures increase moderately in number during the first week, reaching a peak on the seventh day, and decreasing thereafter. Giant-sized tumor cells are first seen in significant numbers on the fourth day; they increase rapidly, reaching a peak on the thirteenth day, and then decrease in number at a slower rate. In an occasional radioresistant tumor, giant-sized tumor cells are found in conjunction with abnormal mitoses during the fifth to the eighth week.

The above observations suggest that as a result of irradiation there is a pattern of progression from normal mitotic figures to abnormal mitotic figures to giant-sized tumor cells to profound nuclear disturbances. In radiosensitive tumors, these events occur during the first few weeks; in radioresistant tumors they take place at a later time and are milder in degree.

Some authors have considered these giant-sized cells to be mutation forms resulting from radiation-induced chromosome alterations. According to genetic laws, some of these abnormal forms should perpetuate themselves in persistent radioresistant tumors or in recurrences. However, the progressive disappearance, for the most part in a few weeks, of these giant-sized tumor cells would seem to indicate that they are degenerative, dying mutation forms. It is well known that

A. Appearance before treatment. Note tendency toward multinucleation. In the multinuclear cells, the nuclei are similar in appearance to those of the mononuclear cells. ×*c*.300

B. Biopsy on 7th day. Early radiation changes in the form of enlargement and distortion of the nuclei. Many cells are enlarged, due to cytoplasmic swelling, and are causing compression and pyknosis of a few cells. ×*c*.300

C. Biopsy on 14th day. Striking example of giant-sized tumor cells due to cytoplasmic changes as well as nuclear aberrations. In the cytoplasm can be seen changes progressing from swelling to minute vacuolation to large vacuoles. ×*c*.300

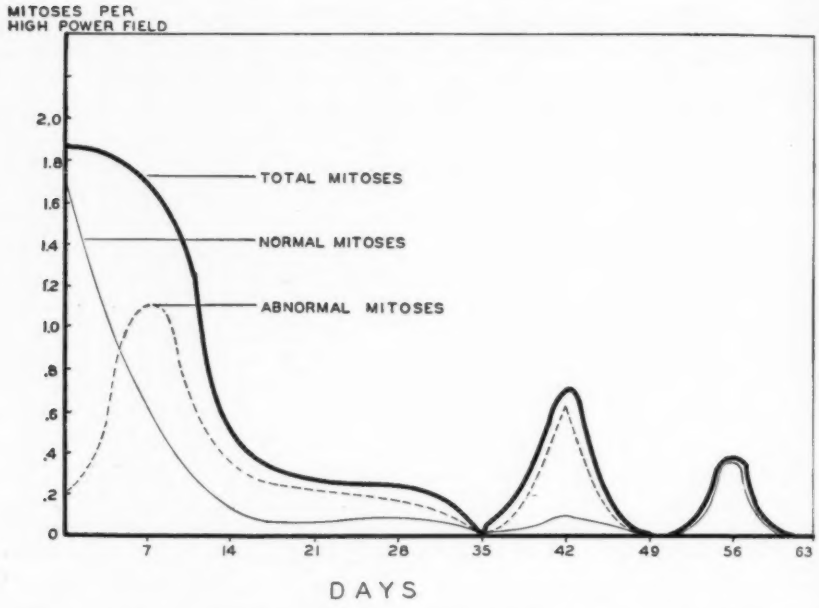


Fig. 6. Study of normal and abnormal (radiation-induced) mitotic figures. Points on curve represent average of all cases in this series. During the first two weeks, as the normal tumor mitoses decrease, the abnormal radiation-induced mitoses increase. Two radioresistant lesions raised the average in the 6th and 8th weeks.

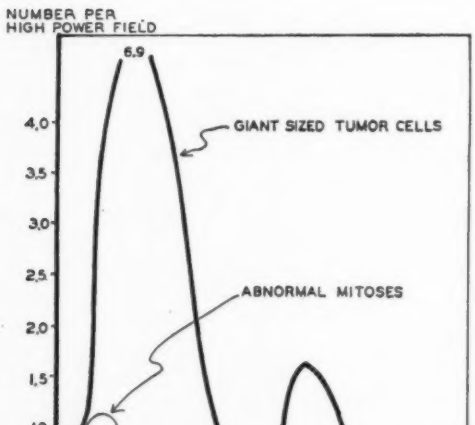


Fig. 7. Relationship between time of appearance of radiation-induced abnormal mitotic figures and giant-sized tumor cells (mutation forms). Points on curves represent average of all cases in this series. Reduction in number of abnormal mitotic figures is succeeded by a marked increase in number of giant-sized tumor cells.

certain recurrent tumors may differ slightly in appearance from the primary tumor. There is no evidence to show whether these differences are the result of mutation changes or of other environmental influences such as changes in the tumor bed.

Cells containing radiation-induced abnormal mitotic figures either undergo destruction or complete the process of cell division with the formation of abnormal, bizarre, daughter cells that are incapable of perpetuation. These bizarre cells exhibit the following distortions: lobated nuclei, multinucleation, and giant-sized, frequently hyperchromatic, nuclei. Lobated nuclei are probably the end-product of radiation-induced abnormal mitotic figures (Fig. 5, c).

*Multinucleated Cells:* The appearance of multinucleated cells may have three possible explanations: they may be explained by a mild form of damage to the nucleus directly; they may be the result of injury in an early phase of mitosis; or they may represent an accentuation of the pre-

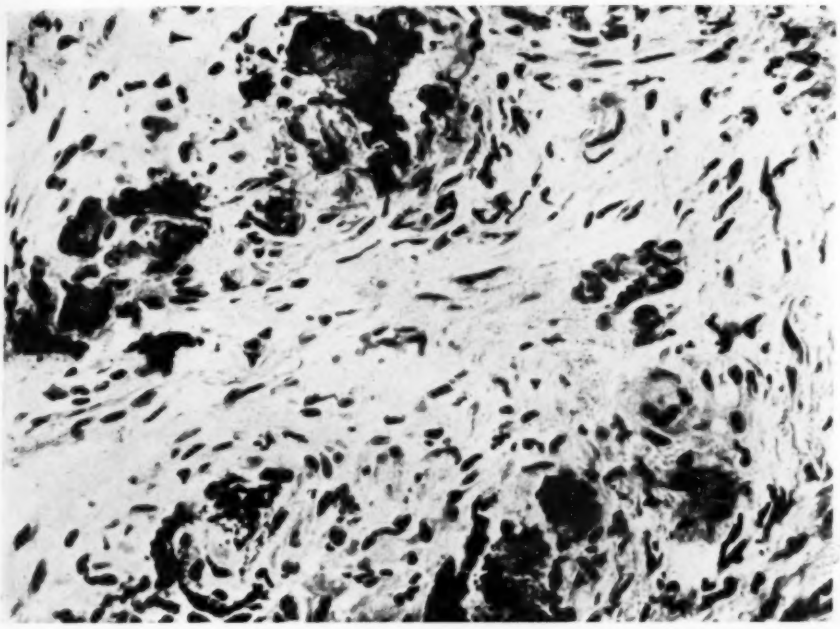

Fig. 8. Biopsy on 24th day, showing areas of calcification in the stroma. ×375

existing tendency of a tumor to form multinucleated cells (Fig. 5). Concerning the latter, it is observed that radiation-induced multinucleated cells are most commonly seen in anaplastic tumors having multinucleated cells before irradiation. Following irradiation, the number of nuclei per cell and the number of multinucleated cells are increased. These nuclei are often normal in appearance, and show fewer radiation changes than are seen in a mononuclear tumor cell, suggesting that the destructive effect is expended against the process of cell division rather than the cell itself.

### *Calcification*

Although some authors describe calcification of tumor cells as a common radiation effect, it was not prominent in our material.

Melnick (1) irradiated the Flexner-Jobling rat carcinoma and the Jensen rat sarcoma and in some of the tumors found "surviving tumor cells all transformed, under various forms of fractional doses, into a pure growth of abnormal, hyperchromatic giant cells. These abnormal cells degenerated in a specific manner by calcification of the nucleus." Melnick and Halley (2), in studying human breast carcinomas that were irradiated preoperatively, found that after the most sensitive cells were destroyed, the remaining cells underwent mutation to an abnormal giant-sized cell that degenerated not by necrosis but by calcification of the nucleus. On the other hand, Warren *et al.* (7) and Schmitz and his associates (8), in studying the effect of irradiation on squamous-cell carcinoma of the uterine cervix, did not mention calcification as one of the changes.

Calcification was not found in our material as a significant change. Small amounts of calcium were seen in one tumor in the center of a few keratin masses on the fourteenth day; in another a few small masses of calcium were present in the dense connective-tissue stroma on the twenty-fourth day (Fig. 8). It could not be determined whether this represented

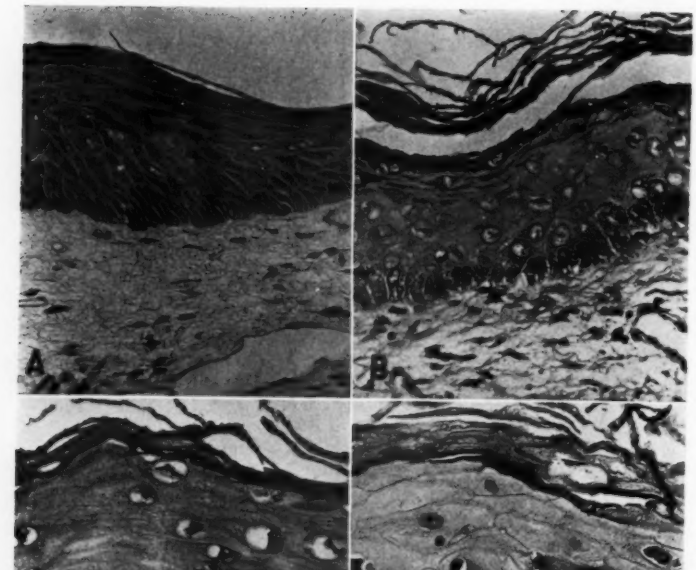


Fig. 9. Study of radiation keratogenesis of normal skin overlying a carcinoma of the breast that received a daily skin dose of 266 r, and a total skin dose of 5,332 r in 24 days.

A. Normal skin before irradiation. ×225

B. Biopsy on 12th day. Skin dose 2,926 r. Increased keratinization with slight increase in thickness of the epidermis. ×225

C. Biopsy on 19th day. Skin dose 4,522 r. Progressive keratinization and swelling of cells with increased thickness of epidermis. Basal cells are becoming keratinized. ×225

D. Biopsy on 23rd day. Skin dose 5,106 r. Progressive swelling and keratinization. Disruption of the basal layer and inflammatory cell response in the underlying corium are preliminary to total desquamation of the epidermis. ×225

E. Biopsy on 23rd day. Another area reveals separation of keratinized epidermis and partial desquamation. ×225

F. Biopsy on 38th day, fourteen days after a total skin dose of 5,332 r. Complete desquamation of epidermis with fibrino-cellular reaction. ×225

calcification of tumor cells or of keratin masses.

### *Radiation Keratogenesis*

The third method whereby normal squamous epithelium and squamous-cell carcinoma are destroyed by irradiation is through the process of *radiation keratogenesis*. This process occurs less often than acute cell death or giant-sized tumor cell formation, and is probably the least important mechanism of radiation injury.

Radiation keratogenesis is the acceleration either in rate or degree of the normal process of keratinization. It is a cytoplasmic phenomenon, although the process might be activated by the effect of radiation on the nucleus. Those nuclear changes observed in association with radiation keratogenesis are either secondary to keratinization of the cytoplasm or are the result of the direct action of radiation on the nucleus, as described previously. The actual time required for the basal cell of normal stratified squamous epithelium to differentiate and keratinize is not definitely known. It probably varies in different regions of the body.

*Radiation Keratogenesis of Normal Skin:* Irradiation of normal skin will accelerate the process of keratinization. Keratinization progressively involves the deeper layers of irradiated epithelium so that prickle cells and finally basal cells become keratinized. When the latter become fully keratinized, the epidermis begins to separate from the corium and finally desquamates.

The process of radiation keratogenesis is illustrated in Figure 9, A to F. On the twelfth day after the first treatment (Fig. 9, B), there is an increase of the thickness of the entire epidermis. The stratum corneum is moderately increased in thickness due to the accumulation of additional layers of keratinized cells from the underlying strata. The cells of the prickle-cell layer are slightly swollen and their intercellular bridges are less prominent. These swollen prickle cells also show early diffuse keratinization. The nuclei of the cells of all the layers are swollen, with a loss of peripheral chromatin material. On the nineteenth day (Fig. 9, C), there is a marked increase in thickness of the epidermis, due chiefly to swelling of cells, though there is an actual decrease of the number of layers of cells as a result of desquamation of some hornified cells. All cells below the stratum corneum are swollen and show progressive degeneration, with the formation of large vacuoles. Keratinization is now present in all layers, including some of the basal cells. The well demarcated thickened stratum corneum is manifested clinically at this stage by a brownish discoloration, and the superficial layer of the skin can be partly peeled off in fine flakes. This should not be confused with the late deposition of pigment in the corium following the subsidence of a first-degree erythema. On the twenty-third day, at the height of the skin reaction, there is further swelling of the cells, combined with diffuse keratinization of the cytoplasm (Fig. 9, D); the cytoplasmic material of contiguous cells commences to fuse; the nuclei have undergone further degenerative changes, with disappearance of some of them; the basal layer presents similar changes and has become almost unrecognizable as a separate layer. At the same time (Fig. 9, E), other areas may be completely keratinized, with early separation of the keratinized basal cells from the underlying corium. By the thirty-eighth day (Fig. 9, F), there are complete desquamation of the keratinized epidermis and replacement with a pseudodiphtheritic membrane.

*Radiation Keratogenesis of Normal Mucosa:* Early during the course of fractionated irradiation, there appears on the irradiated oral mucosa a membrane-like white layer over the hard palate (Fig. 10), buccal mucosa, gums, and tongue. The white layer becomes progressively denser and eventually represents an area of radiation-induced leukoplakia. It is uniform and smooth. Its thickness may depend on many factors: individual susceptibility, tissue susceptibility, amount of irradiation,

Fig. 10. Radiation-induced leukoplakia of normal hard palate and edentulous alveolar ridge. Note absence of this phenomenon in the non-keratinizing epithelium of the retromolar fossa.

and distribution in time of the radiation dose.

The regions where radiation-induced leukoplakia develops correspond to the regions that Coutard said were covered with a keratinizing type of epithelium from which radioresistant tumors are prone to develop. These areas are the hard palate, gums, buccal mucosa, and dorsum of the tongue. This membrane appears on the twelfth to the eighteenth day after the first treatment and becomes progressively more intense.

In other areas exposed to similar amounts of radiation, as the faucial arch (uvula, soft palate, anterior tonsillar pillars), floor of the mouth, under-surface of the tongue, retromolar area (Fig. 10), oropharynx, and hypopharynx, radiation leukoplakia does not develop. These areas are covered with a so-called non-keratinizing type of mucosa, and in general give rise to more radiosensitive carcinomas.

The more radiosensitive the tissue, the earlier will it respond to irradiation. For example, the average time of appearance of the second-degree epithelitis with denudation of the mucosa is the fourteenth day. Keratinizing epithelium, though receiving the same dose of radiation as the non-keratinizing epithelium, will behave like radioresistant skin (Fig. 1), in that reactions will begin later and generally be milder in degree. Thus, on the fourteenth day, when the non-keratinizing mucosa is becoming denuded, the radiation leukoplakia in the keratinizing mucosa is just commencing. When the mucosal epithelitis approaches a third-degree intensity, on or about the twenty-fifth day (Fig. 1), the keratinizing mucosa or the skin may still show only mild or moderate keratogenesis with thickening of the stratum corneum, as in Figure 9, c.

Radiation keratogenesis of mucous membrane and anal skin is observed clinically as a white membrane. In the skin of the remaining portions of the body, it appears as a brownish, superficial, parchment-like membrane, due to the thickened stratum corneum.

*Radiation Keratogenesis of Tumor Cells:* Tumor cells of a squamous-cell carcinoma may undergo radiation destruction through the process of radiation keratogenesis. This effect is similar to that observed in stratified squamous epithelium of normal skin and mucosa. Keratinization of the cytoplasm in the tumor cell proceeds to completion; the nucleus becomes compressed and pyknotic, and the cell becomes mummified and is desquamated.

Although a few writers have observed increased keratinization following irradiation, the role of radiation keratogenesis as a mechanism of cell destruction has not been stressed. In an occasional tumor, radiation keratogenesis may be the dominant mechanism of cell destruction. However, the process is seen in varying degrees in most irradiated squamous-cell carcinomas. Its rate and amount depend on three factors: inherent tendency of the tumor cell to keratinize, radiosensitivity of the tumor cell, and size of the daily radiation dose.

Occasionally radiation keratogenesis occurs very early during treatment. This process is well illustrated in Figure 11, showing a moderately well differentiated squamous-cell carcinoma of the floor of the mouth, with central keratinization involving approximately 15 per cent of the cells (Fig. 11, A). Forty-eight hours

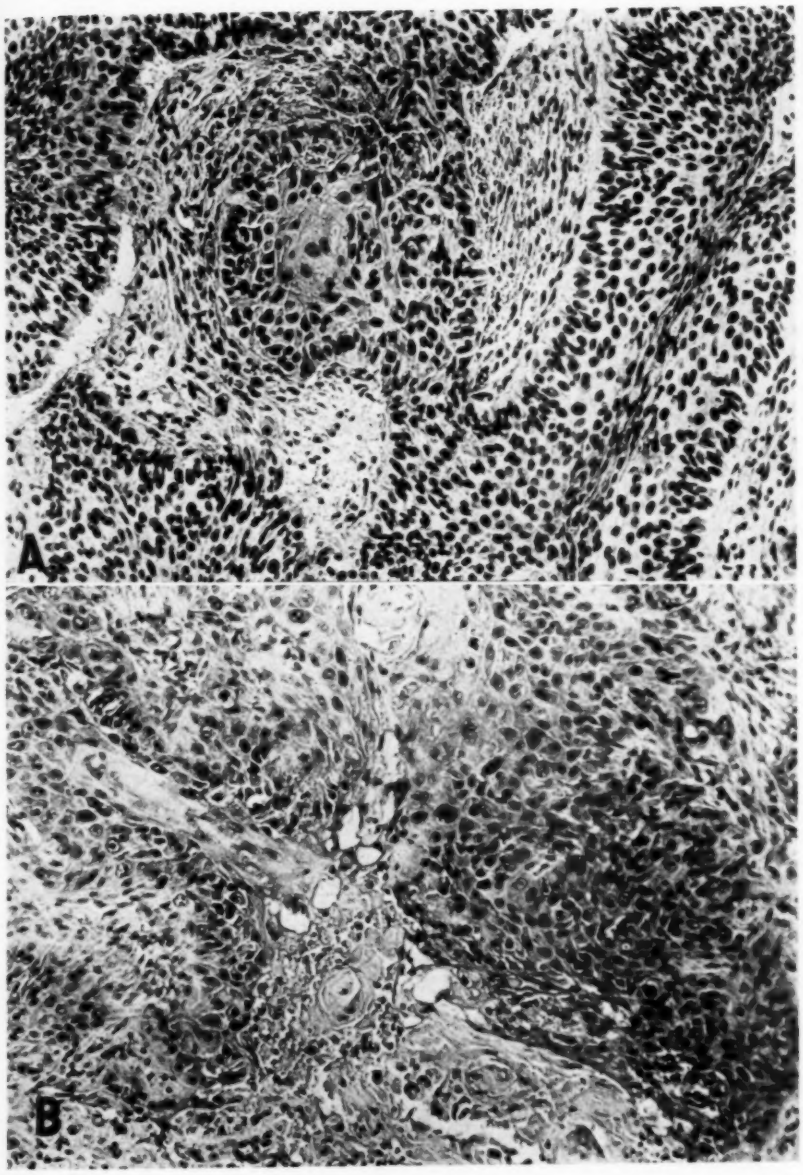


Fig. 11, A and B. Squamous-cell carcinoma, with moderate differentiation, destroyed almost exclusively by the process of radiation keratogenesis.

A. Biopsy before treatment. Approximately 15 per cent of the cells are keratinizing. ×*c*.180

B. Biopsy 48 hours after first treatment. Marked increase of keratinization. At this time approximately 50 per cent of the cells are keratinizing. ×*c*.180. See also Figure 11, C and D.

after the first treatment, there is a marked increase of keratinization, that now involves approximately 50 per cent of the cells (Fig. 11, B). In areas where keratinization is most marked, many additional cells of the prickle-cell layer have become

keratinized. Some of the completely keratinized areas contain solid keratin masses. In the other areas, many of the cell layers escape keratinization. In association with and probably secondary to irregular keratinization, there is some loss of stratification.

On the ninth day, the process of keratinization has involved almost all the tumor cells. The tumor has shrunken approximately 25 per cent in volume and has lost approximately 35 per cent of the cells histologically. However, the percentage of keratinized tumor cells has increased from 15 to 95 per cent, and most of these remaining cells are non-viable (Fig. 11, C). Only the peripheral layer of basal cells circumscribing some islands of tumor cells is non-keratinized. The remaining cells show all gradations of keratinization. As the process progresses, the nucleus is compressed, reduced in size, and finally disappears. The cell is now completely keratinized and mummified.

These cells may be desquamated from the surface of the tumor or, if deeply located, may remain in the tumor bed as solid keratin masses (Fig. 11, D). Later, multinucleated foreign-body giant cells surround the keratin masses for the purpose of phagocytosis. In all probability, this is the only reason for the presence of multinucleated foreign-body giant cells in irradiated squamous epithelium.

In 8 of the 24 tumors of this series treated with an effective daily tumor dose of radiation (approximately 275 r), there was a significant increase of radiation keratogenesis. In 4 of these 8, radiation keratogenesis played the dominant role in the destruction of the tumor. In the remaining 4, this process played a minor role in tumor destruction.

Radiation keratogenesis was most prominent in tumors with slight to moderate keratinization and classified as grade 2. This again confirms the principle that the characteristic histologic features of a tumor are often intensified and accelerated by irradiation. The unexpected radiosensitivity of an occasional grade 2 squamous-cell carcinoma may be due to destruction through the process of radiation keratogenesis. This may explain some errors in the histologic estimation of the radiosensitivity of a tumor.

All 4 cases that were purposely underirradiated, with one-half of the usual daily tumor dose (135 r), showed increased though mild radiation keratogenesis. The process in these instances was one of maturation of keratinizing cells rather than complete destruction of the tumor cells (Fig. 14).

In 11 of the 28 cases, multinucleated foreign-body giant cells were found in close apposition to keratin masses that they were phagocytizing. There was considerable variation in the time of appearance of these giant cells. They were first noted on the fourteenth day after onset of treatment, were present during the third and fourth weeks, and occasionally as late as the seventh week.

*Spontaneous Desquamative Keratinization:* Occasionally, an untreated tumor cell, in the course of normal maturation, will rapidly change from a pre-keratinizing polyhedral cell to a completely keratinized cell that is promptly desquamated into the stroma and becomes surrounded by foreign-body giant cells. This was seen in the "before-treatment" biopsies of two tumors. In one of these cases (Fig. 13), radiation keratogenesis played a dominant role in the destruction of the tumor, which was radiosensitive; in the other (Figs. 1 and 12), the tumor was extremely radiosensitive, and the second biopsy, taken on the tenth day, showed only 5 per cent of the tumor cells remaining, and more than half of these were keratinized. Although acute cell death played an important role in the destruction of the large transitional-cell component of the tumor, radiation keratogenesis also contributed to the destruction of cells.

These two cases suggest that a tumor having spontaneous desquamative keratogenesis before treatment is likely to reveal accelerated radiation keratogenesis. Spontaneous keratogenesis in the original biopsy specimen, therefore, may be an index of

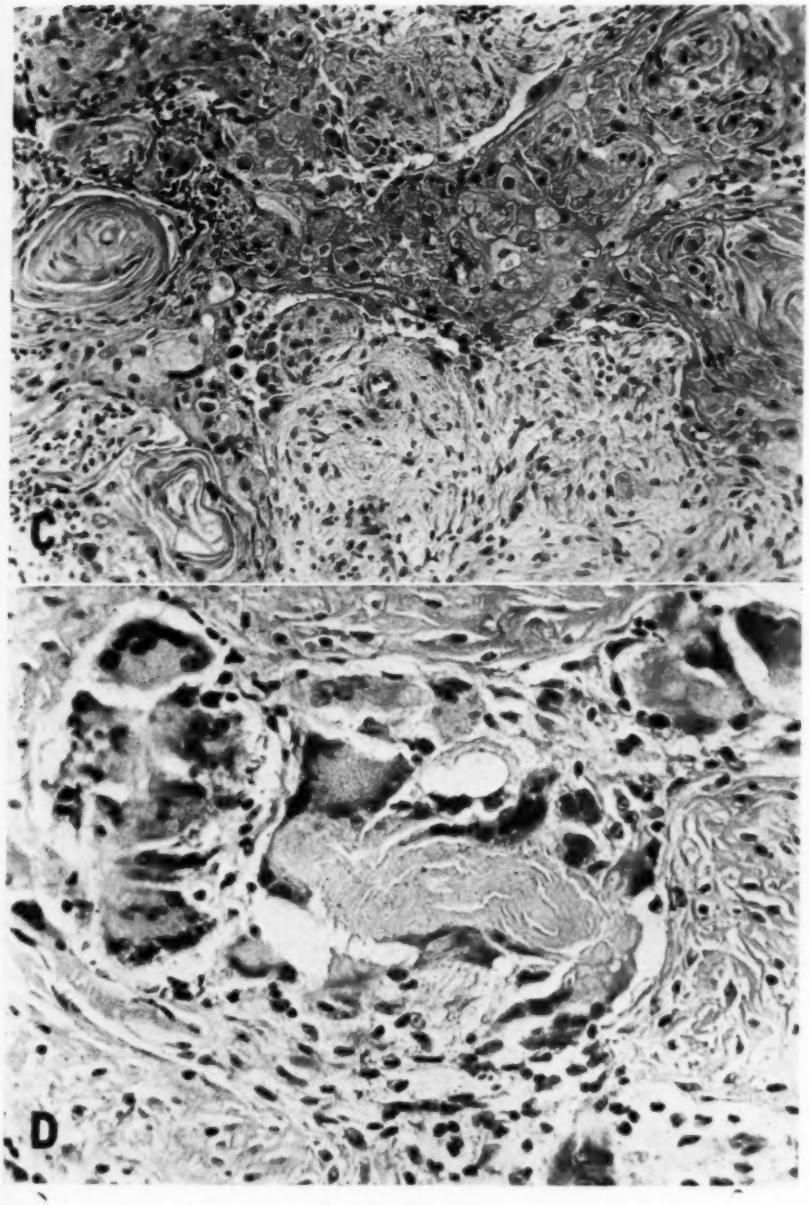


Fig. 11, C and D. Same tumor as shown in Figure 11, A and B.
C. Biopsy on 9th day. Practically all residual tumor cells are keratinizing or keratinized. ×c.180
D. Biopsy on 35th day. Tissue removed from the tumor at this time reveals only masses of keratin surrounded by multinucleated foreign-body giant cells.

radiosensitivity. This observation provides additional evidence that a physiologically active cell—in this instance, active keratin production in the cytoplasm—may be as radiosensitive as reproductively active cells with numerous mitoses.

*Maturation of a Tumor Due to Under-Irradiation*

In previous clincial studies of skin reaction and tumor shrinkage rates (4, 5), it was observed that, when a small daily dose of roentgen rays was administered over an extended period of time, a peculiar phenomenon occurred (Fig. 2). At the beginning of the fifth week of treatment, skin and mucosal reactions began to heal in spite of continued irradiation. Apparently, normal stratified squamous epithelium is able to protect itself by means of a recovery process and to acquire the ability to withstand radiation bombardment. The exact mechanism is unknown, although a number of factors participate.

The study of tumors treated with one-half the optimum effective daily tumor dose (*i.e.*, 135 r) indicated that a tumor, when under-irradiated, might also adapt itself to the destructive effect of radiation. During this recovery phase the tumor may become more mature histologically.

This process of maturation is illustrated in Figure 14. The original tumor (Fig. 14, A) was an undifferentiated carcinoma of the tonsil. The tumor was purposely under-irradiated, with a daily tumor dose of 135 r. On the twenty-first day (Fig. 14, B) there was slight destruction of the tumor, but the remaining cells were grouped in islands and had begun to show early stratification, central keratinization, and a few intercellular bridges. A few of the remaining cells had been injured by the radiation as indicated by the formation of giant-sized tumor cells. The stroma had become more adult in type. On the forty-second day—at which time the skin and mucosal reactions had healed in spite of continued daily irradiation—the maturation of the tumor had become marked (Fig. 14, C). There was no further tumor destruction, but increased stratification and more advanced keratinization. How much of the latter represented maturation and how much represented radiation keratogenesis could not be determined. At this time, the tumor had shrunken 50 per cent in volume. Many of the cells were viable, as the tumor resumed active growth shortly thereafter. This is a typical example of the true maturation of a tumor that has received an inadequate daily dose of radiation.

There is an optimum daily dose and an optimum time period in an efficient course of irradiation of a tumor. The common practice of avoiding severe local and general x-ray reactions by reducing the daily dose and extending the treatment over an unusually long period of time, such as two months, is inefficient. During the second month of treatment, recovery phenomena dominate radiation reactions. The tumor may mature and thereby acquire increased radioresistance. It is probable that increased maturity of the tumor and decreased vascularity of the stroma further contribute to radioresistance.

Occasionally, during the recovery phase (twenty-eighth to forty-second day) of an under-irradiated tumor, regrowth may be observed during irradiation without histologic maturation of the neoplasm.

The above statements refer to squamous-cell carcinoma. For other tumors there are probably specific values for optimum daily dosage and total period of irradiation.

*Changes in Stroma*

The effect of irradiation on the stroma of a tumor has been the subject of considerable investigation and discussion. The term stroma is applied to the connective-tissue framework and blood vessels supporting and nourishing the tumor cells; whereas the term "tumor bed" is applied to surrounding normal tissues in which the tumor is located. The following discussion is confined to stromal changes.

The changes to be described are those seen in the connective-tissue stroma intimately related to the tumor cells. From our observations, stromal changes appear to be reactive phenomena secondary to the destruction of the tumor cells. These changes are: replacement fibrosis, maturation of connective-tissue fibers and, to a

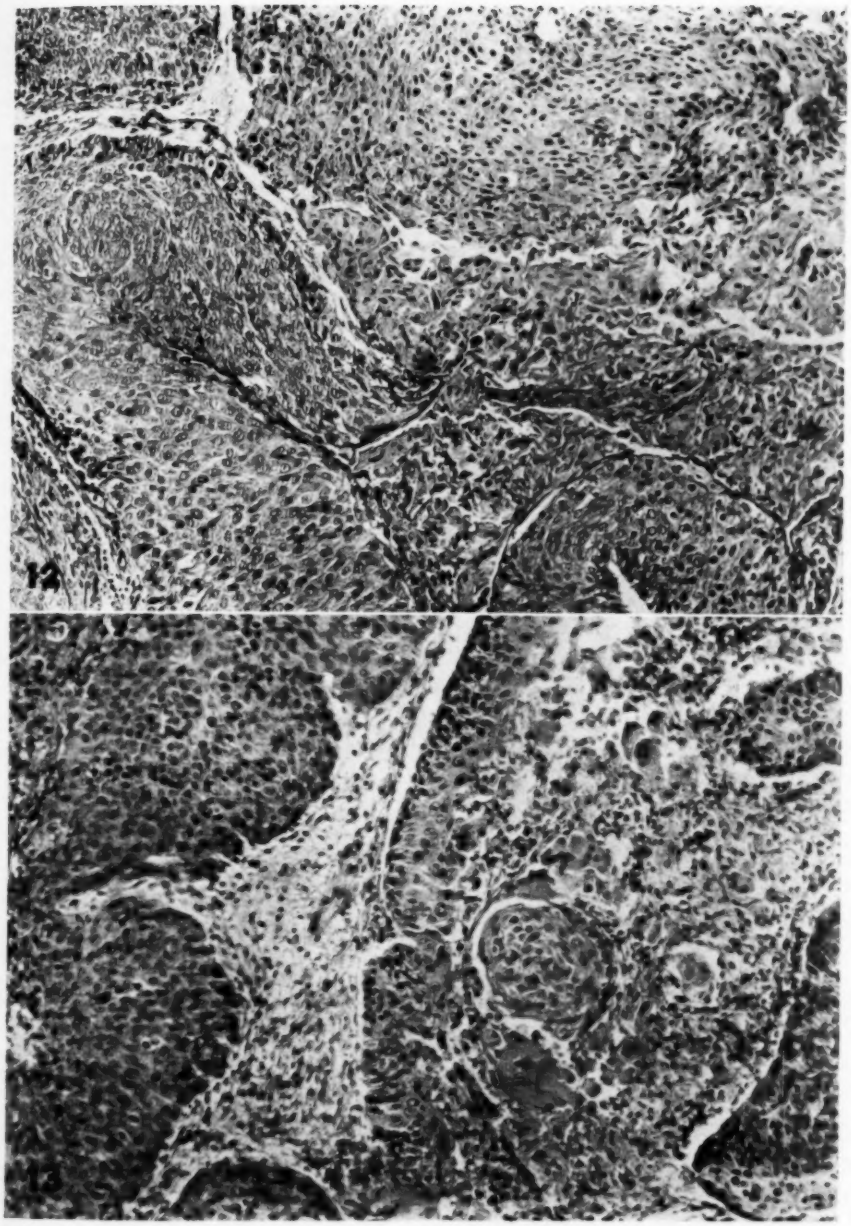

Fig. 12. Spontaneous keratogenesis in a tumor. Moderately undifferentiated squamous-cell carcinoma of the tonsillar pillar, before irradiation. Desquamation of completely parakeratinized cells into tumor interstices in upper right corner of photograph. ×*c*.145

Fig. 13. Spontaneous keratogenesis in a tumor. Squamous-cell carcinoma with varying degrees of differentiation, before irradiation. Desquamation of keratinized cells and keratin masses into the stroma, with a foreign-body giant cell reaction. ×*c*.145

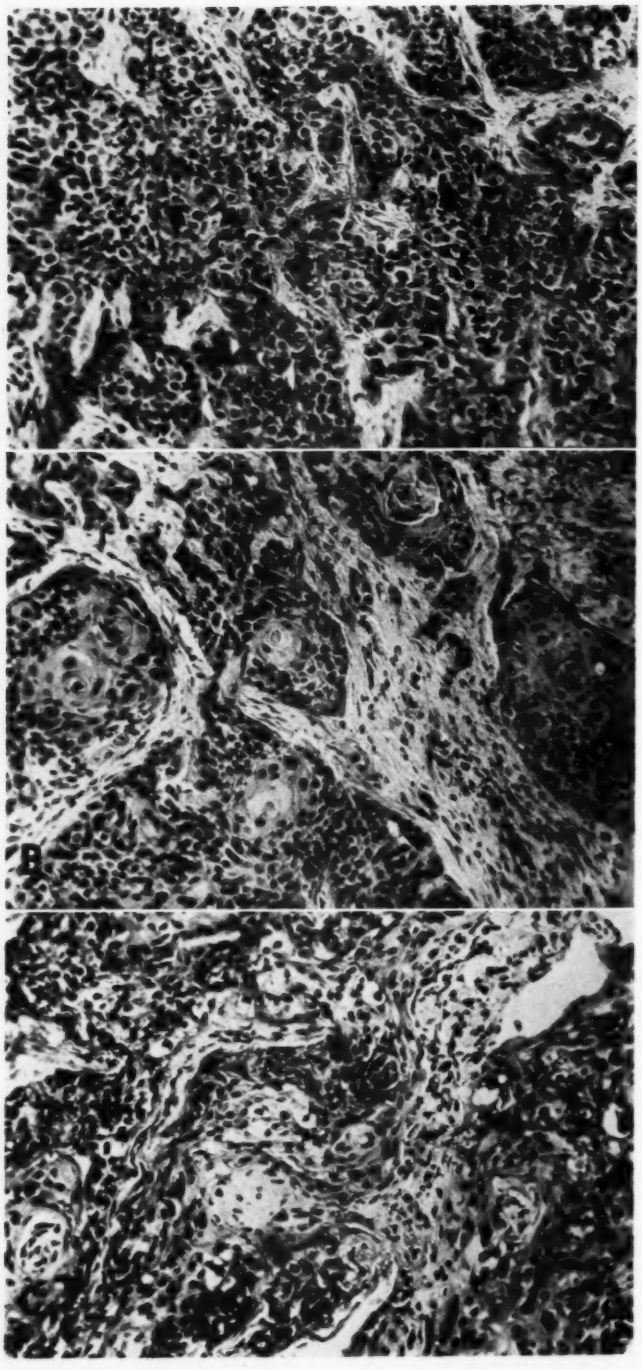


Fig. 14. Undifferentiated carcinoma of tonsil, irradiated with inadequate daily tumor dose of 135 r (see Fig. 2).

A. Appearance before treatment. There is no keratinization or stratification. ×*c*.130

[*Legend continued on opposite page*]

lesser extent, primary degenerative changes and nuclear alterations in the connective-tissue cells.

In a radiosensitive cellular tumor (Fig. 15, A), the early disappearance of cells by lysis (acute cell death) exposes to view the underlying connective-tissue stroma. Thus toward the end of the first week, there are seen areas of loose adult connective tissue that were originally obscured by tumor cells (Fig. 15, B). The adult connective-tissue cells are characteristically spindle-shaped and have oval or spindle-shaped, darkly staining nuclei. Many thin collagen fibers are present. By the tenth day, however, there may be observed beginning proliferation of new connective tissue in the form of young fibroblasts growing into the areas formerly occupied by tumor cells. This proliferation proceeds despite the fact that by this time the cumulative destructive effect of the daily fractional doses of radiation has reached a high intensity, sufficient to produce a second-degree reaction in the adjacent normal mucosa. Thereafter the stroma becomes progressively denser, due chiefly to proliferation of fibroblasts but also to condensation of the pre-existing adult connective-tissue cells. On the fourteenth day (Fig. 15, C), there may be seen numerous moderately large areas of these young fibroblasts, some of which are maturing. Between the fourteenth and twenty-first days the changes in the stroma just described are detectable clinically when the biopsy punch or scalpel encounters difficulty in cutting through the dense fibrous tissue. Between the twenty-first and twenty-eighth days, the connective tissue progressively matures so that finally there is a dense stroma composed of hyalinized connective tissue (Fig. 15, D and E).

In studying the effect of radiation on the stroma, the question arises as to whether the rate of replacement fibrosis is accelerated, retarded, or unchanged during irradiation. A surgical wound will heal by the proliferation of young fibroblastic tissue in approximately five days. However, in an area of destroyed tumor cells, replacement fibrosis may require ten to fourteen days to attain the same stage. This period of delay is not quite so long as the above figures would indicate, because there is a latent period following irradiation exposure, before tumor destruction occurs and replacement fibrosis ensues. Nevertheless, the process of replacement fibrosis following radiation destruction of tumor cells appears to be retarded.

The rate and stage of replacement fibrosis depend upon the rate of destruction of the tumor cells. The more radiosensitive tumor cells will degenerate early and soon be replaced by fibrous tissue. The less sensitive cells degenerate more slowly, and replacement fibrosis is delayed. Consequently, in most tumors that contain cells having different degrees of radiosensitivity, a particular biopsy specimen taken after irradiation may show all stages of fibrosis. Thus, in Figure 15, E, taken from a relatively radiosensitive tumor, there has occurred early acute cell death with replacement of tumor by fibroblastic tissue that shows beginning hyalinization. Figure 15, D, represents another less radiosensitive area of the same specimen, wherein the tumor cells did not degenerate simultaneously. There is seen a central island of residual tumor cells undergoing destructive changes; surrounding this, in a zone where tumor cell destruction occurred previously, young fibroblasts are proliferating. The periph-

B. Biopsy on 21st day. Tumor dose approximately 2,000 r. A few peripheral cells of each cell mass have been destroyed. There are early central keratinization and slight stratification. ×*c*.130

C. Biopsy on 42nd day. Tumor dose approximately 5,100 r. The appearance of the tumor is materially different from the original biopsy specimen. There are stratification and increased keratinization. This is an example of a tumor maturing when exposed to prolonged inadequate irradiation. ×*c*.130

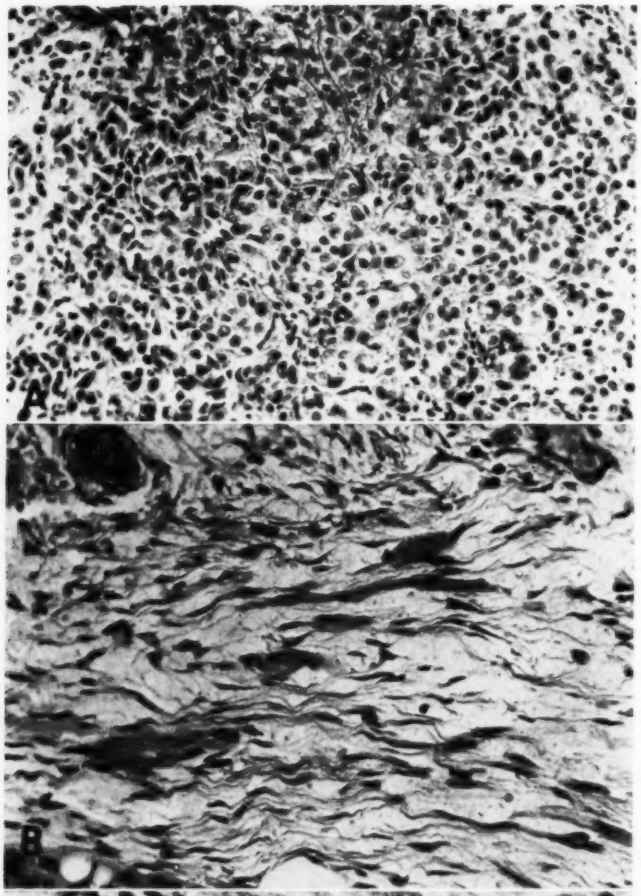


Fig. 15, A-C. Progressive stromal changes occurring in an undifferentiated squamous-cell carcinoma. See also Fig. 15, D–F. A. Appearance before irradiation. ×250 [*Legend continued on opposite page*]

eral zone was the site where tumor cells were first destroyed and this is now occupied by mature connective tissue. In a radioresistant tumor, there may be little replacement fibrosis because there has been little degeneration of tumor cells.

The dominant stromal changes described above are secondary in nature, being those of replacement and reparative fibrosis. Melnick and Bachem (1) found no direct changes in the stromal cells, when irradiating transplantable tumors with roentgen rays. There did occur in some of our cases, however, a direct destructive effect on the connective-tissue cells and collagen fibers (Fig. 15, F), both in the connective tissue of the tumor bed and in the replacement connective tissue, in their various stages of development. These changes consisted of swelling of the young fibroblasts and occasionally of the more mature connective-tissue cells; slight to moderate vacuolation of the cytoplasm and the nucleus. Infrequently, other degenerative changes were seen in the nucleus of stromal cells, such as pyknosis, karyorrhexis and karolysis; swelling and fragmentation of the collagen fibers; and, in one instance, multinucleated fibroblasts (Fig. 15, C).

Although various combinations of these primary changes in stromal cells were observed in 16 of the 28 cases, they were generally mild in degree and affected a small percentage of the cells. These changes first appeared on the seventh to tenth day and were most prominent during the interval from the fifteenth to the twenty-fifth day. Apparently the cumulative radiation dose must be large before the ordinarily radioresistant connective-tissue cells can be injured.

In addition to the direct destructive effect of radiation on the tumor cells, it is contended by some that residual radioresistant tumor cells become incarcerated in a dense, hyalinized connective-tissue bed. This tissue is alleged to undergo progressive contracture resulting in asphyxiation destruction of some of the tumor cells. It is our impression that the connective tissue plays little if any part in the destruction of the tumor cells themselves, but is predominantly a replacement fibrosis. Somewhat confusing in this picture is the term, abortive fibrosis, introduced by Ewing (10). He was describing the occasional finding, as in a heavily irradiated endothelioma of bone, of intact tumor cells in a mass of relatively avascular, hyalinized connective tissue. This is probably an abortive or incomplete radiation effect rather than an attempt on the part of the hyalinized connective tissue to destroy or abort the tumor cells, as interpreted by Ewing.

### *Inflammatory Reaction in Tumor Tissue and Stroma*

Cellular infiltration in the areas of replacement fibrosis, though slight, is composed predominantly of lymphocytes and plasma cells. In later biopsy specimens, when there is moderate to marked destruction of tumor cells, polymorphonuclear leukocytes are present. From a study of our material, we are unable to attribute any special significance to the cellular infiltration other than that associated with destruction and necrosis of tissue. An acute inflammatory reaction is present in the superficial portions of many of these ulcerated tumors.

### *Changes in Muscle*

Radiation damage of the muscle fibers was noted in many of the biopsy specimens that included muscle tissue infiltrated with carcinoma. The changes consisted of marked atrophy, fragmentation of muscle fibers, and swelling with loss of cross-striations. Karyolysis, pyknosis, and even

B. Biopsy on 10th day. Destruction of tumor cells exposes a loosely arrayed adult stroma. ×250

C. Biopsy on 14th day. Young fibroblasts are growing into the areas formerly occupied by tumor cells. Generally these fibroblasts are little affected by radiation. Occasionally, as illustrated above, the cytoplasm and nuclei show fine vacuolation. ×375

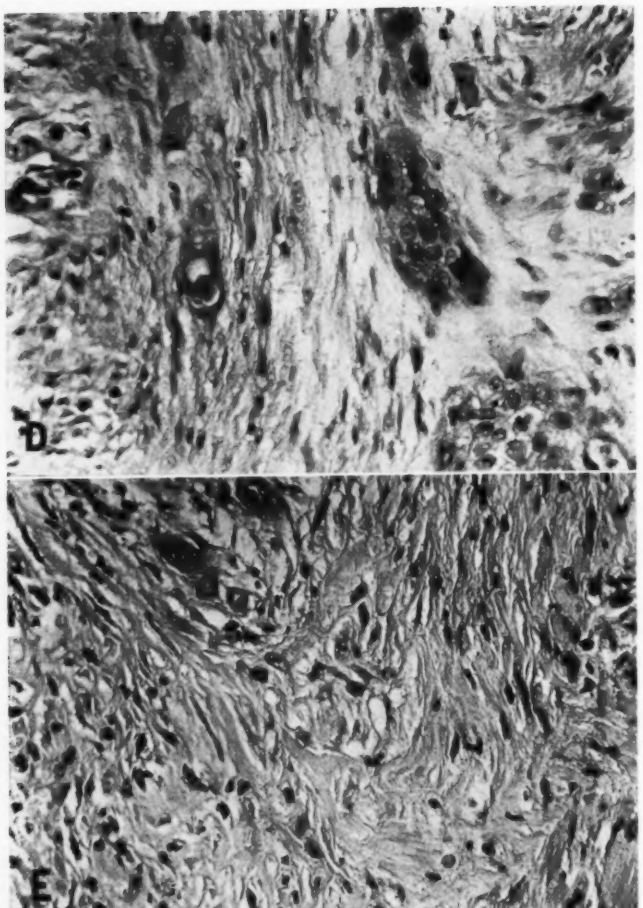


Fig. 15, D–F. Same tumor as shown in Figure 15, A–C.
D. Biopsy on 24th day. Progressive stromal changes, around an island of degenerating tumor cells. There is a zone containing a few fibroblasts, beyond which is seen early hyalinization (upper right corner). ×250 [*Legend continued on opposite page*]

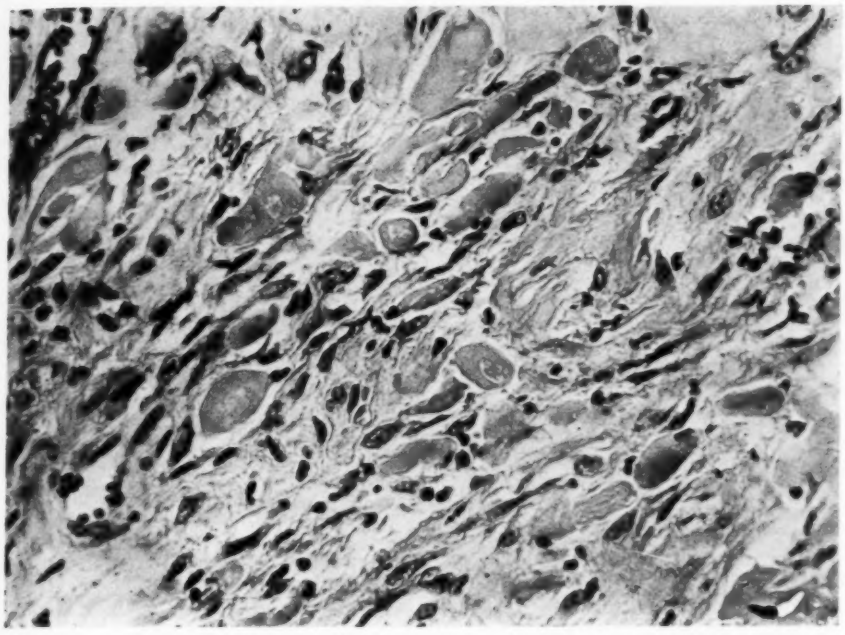

Fig. 16. Degeneration of striated muscle fibers and early replacement of proliferating fibroblasts. ×*c*.335

loss of nuclei were seen in the sarcolemma. Scattered throughout these areas of degenerating muscle fibers were foci of proliferating connective-tissue cells (Fig. 16).

*Blood Vessels*

The importance of the effect of radiation on the blood vessels of a tumor is controversial. The earliest histologic studies, based on the effect of a single massive dose of radium, revealed extensive destruction of blood vessels allegedly resulting in local ischemic necrosis of tissues. Other studies of the late effects of radiation disclosed obliterative endarteritis in varying degree, in association with replacement fibrosis and hyalinization of connective tissues. These and other experimental and clinical observations, such as the relative radiosensitivity of a vascular tumor as compared with the radioresistance of an avascular tumor, led to the conclusion that the effect of radiation on blood vessels was an important mechanism of radiation destruction of a tumor.

Reconsideration of these observations suggests that the single massive dose of radium exercised an overwhelming destructive effect on all types of cells and tissues and had no selective effect.

Cramer (9) found occluded vessels in tumors one week after radium exposure, when active regression was beginning. He concluded that there is a damaging effect of irradiation on the blood vessels both in normal tissues and in animal and human tumors. Ewing (10) and Pullinger (11) also stressed the importance of blood vessel changes as a responsible factor for the death of cells. Pullinger even contended that "all effects following irradiation result from stimulation and degeneration of blood vessels."

On the other hand, Melnick and Bachem

E. Biopsy on 24th day. Another area composed of dense connective tissue in which there is pronounced hyalinization. ×250

F. Biopsy on 28th day. Swelling and fragmentation of collagen fibers in replacement connective tissue. ×375

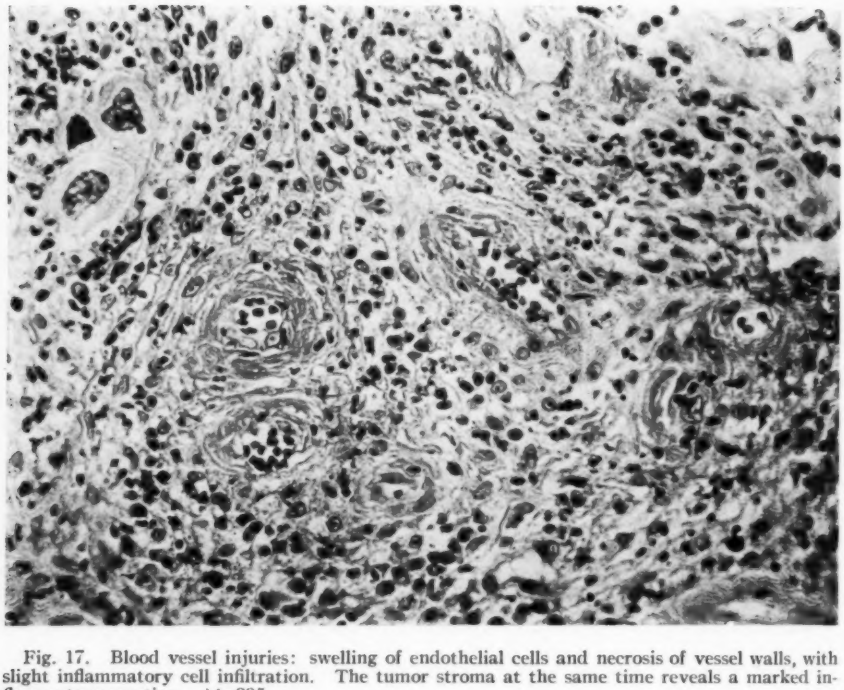

Fig. 17. Blood vessel injuries: swelling of endothelial cells and necrosis of vessel walls, with slight inflammatory cell infiltration. The tumor stroma at the same time reveals a marked inflammatory reaction. ×*c*.335

(1) concluded that all the evidence speaks for a primary action of the radiation on the tumor cells, and not on the stroma. They found no changes in the blood vessels of connective tissue after the administration of doses as large as 12 to 15 skin erythema doses (6,300 to 7,975 r).

After making a preliminary survey of the tissue sections, it was our impression that fractionated external irradiation produced only minimal changes in the blood vessels of the tumor. However, subsequent detailed analysis of each section, including a determination of the number of vessels affected, the type of vessel and the type of changes produced, indicated that radiation damage to vessels was present to some degree in almost every instance.

The changes resulting from radiation injury of blood vessels have been described by many investigators. These changes are: swelling of the endothelial cells, mostly of the capillaries and only occasionally of the arterioles and small arteries; dilatation of the capillaries; necrosis of the walls of capillaries, venules, and arterioles, frequently accompanied by infiltration of their walls by polymorphonuclear leukocytes; thrombosis of arterioles and small arteries, usually associated with necrosis of the vessel wall or marked thickening of the wall (Fig. 17). The most common finding in our material was dilatation of the capillaries with swelling of their endothelial cells. This was observed at various times during irradiation up to the twenty-eighth day, and occasionally after irradiation. The other changes occurred at various times during and after treatment. They were frequently focal in nature, so that in a single section, many vessels appeared normal and only a few revealed the above-mentioned changes. Occasionally, areas of degenerated tumor cells were associated with vessels showing severe radiation changes. This would suggest that focal degeneration of tumor cells may occur not only as a direct effect of radiation upon the cells, but also as a result of an indirect

effect through damage to the blood vessels.

Of 22 tumors whose blood vessels were studied, minimal changes were found in 3; slight to moderate in 14; and marked in 5. From the analysis of this small group we can draw no conclusion as to the relationship between radiosensitivity of the tumor and vascular damage.

### *Practical Application of Serial Biopsies*

Fractionated roentgen therapy is, as a rule, administered over a period of twenty-three to twenty-eight days. It is important to know, early in the course of treatment, the radiosensitivity of the tumor and the effectiveness of the radiation technic.

In Figure 18 has been plotted the average "clinical" shrinkage curve of the tumors in this series, taken from graphs like that shown in Figure 1. It can be seen that by the eleventh day there is insufficient clinical shrinkage to prognosticate the future behavior of the tumor. Also plotted in Figure 18 is a curve representing the average rate of destruction of the tumor as observed microscopically. These results were obtained by evaluating all the cell changes described previously, but with special emphasis upon the percentage of viable cells in each biopsy specimen. Analysis of the "histologic" curve indicates that between the seventh and eleventh days 25 to 50 per cent of the cells were destroyed. In a tumor that is being effectively destroyed by irradiation, most of this destruction will have taken place by the process of acute cell death, which, in our opinion, is the most significant of all radiation effects. Therefore, a single biopsy taken between the seventh and eleventh day will often demonstrate the effectiveness of the particular radiation technic sufficiently early to permit its alteration, if necessary.

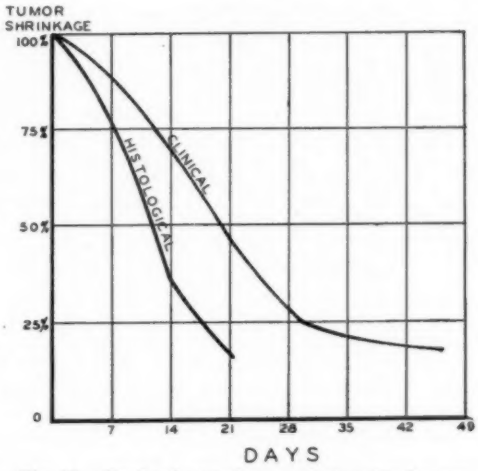


Fig. 18. Study of rate of tumor destruction by comparison of average rate of clinical shrinkage with average rate of histologic destruction in the same series of cases.

## DISCUSSION

Histologically there are a number of methods whereby radiation produces destruction of tumor cells. These processes occur simultaneously, although one type may predominate. Certain features of the primary tumor may determine to some extent the mechanism of radiation destruction, *i.e.*, active keratinization in a tumor may be accelerated by irradiation; pleomorphism and multinucleation, when present in an unirradiated tumor, may be increased under irradiation; the cells of an undifferentiated tumor are prone to undergo acute cell death.

The following is an attempt to classify the numerous radiation effects according to the types of histologic change and the mechanisms of production of such changes.

I. *Histologic Classification*
   1. Acute cell death: Manifested chiefly as lysis of the nucleus and cytoplasm, and to a lesser extent pyknosis and karyorrhexis of the nucleus.
   2. Radiation keratogenesis: An acceleration of the normal process of keratinization.
   3. Progressive enlargement of the cell, with formation of giant-sized tumor cells.
      (*a*) Swelling and vacuolation, probably due to physical-chemical alterations.
      (*b*) Enlargement of the cell with hyperchromatic or vesicular nuclei or multiple nuclei, probably due to chromosome alterations or interference with cell division.
   4. Metaplasia of glandular epithelium and hyperplasia of normal squamous epithelium.[4]

[4] To be described in a future paper.

5. Changes in mitochondria and Golgi bodies (Ludford, 12).

II. *Mechanistic Classification*

1. *Primary Destructive Changes:* These predominate when the cell is radiosensitive or the dose of radiation is large.
   (*a*) Acute cell death.
   (*b*) Delayed cell death.
   (*c*) Destructive changes in connective tissue and blood vessels.
2. *Disruptive Changes:* These occur when the cell is less radiosensitive or when the amount of radiation is relatively small.
   (*a*) Disruption of the reproductive mechanism of the cell, with formation of multinucleated cells or giant-sized tumor cells with large, bizarre, hyperchromatic nuclei.
   (*b*) Disruption of chemical processes. Interference with intracellular and extracellular fluid exchange, probably due to radiation injury to the dialyzing membrane of the cell and nucleus and also to a physical-chemical disturbance of the intercellular and intracellular fluids. This results in diffuse swelling of the cytoplasm, and to a lesser extent of the nucleus, and may account for the formation of vacuoles in the cytoplasm and nucleus.
3. *Acceleration Changes:* Certain biologic processes may be accelerated.
   (*a*) Radiation keratogenesis. The process of keratinization is completed in a shortened period of time. This is both maturation and degeneration.
   (*b*) Untreated tumors, with some mutation forms, such as pleomorphism, hyperchromatism, and multinucleation, will, after irradiation, show these changes to be accentuated.
   (*c*) Accelerated hyalinization of connective tissues.

## CONCLUSIONS

1. The destructive effect of radiation on squamous-cell carcinoma of the mouth and pharynx is achieved by several processes: acute cell death, progressive enlargement of cells to giant-sized tumor cells, and radiation keratogenesis.

2. Acute cell death is the most common change. It affects the cytoplasm, nucleus, and other components of a cell impartially and is usually seen in the first seven days. This is the process whereby the most radiosensitive cells are destroyed. Its importance has not been sufficiently emphasized.

3. The less sensitive cells, not undergoing acute cell death, show progressive enlargement to giant-sized tumor cells. This is accomplished through two different mechanisms: (1) swelling and vacuolation of the cytoplasm and to a lesser extent of the nucleus, probably through a physical-chemical disturbance of the intercellular and intracellular exchange of fluids; (2) disruption of the nuclear function, resulting in the formation of various nuclear abnormalities.

4. Radiation keratogenesis, another mechanism of cell destruction, is the acceleration either in time or degree of the normal process of keratinization. It is a cytoplasmic phenomenon.

5. Under-irradiation of a tumor (chiefly in the form of an inefficiently small daily dose) produces some destruction of tumor cells, but chiefly provokes a maturation of the more radioresistant cells.

6. The most pronounced change in the stroma is replacement fibrosis, secondary to and in proportion to radiation destruction of a tumor. Irradiation also increases hyalinization of the connective-tissue stroma, and, to a slight extent, produces degenerative changes within some fibroblasts, namely swelling and vacuolation.

7. With fractionated irradiation, damage to the blood vessels is usually slight, occasionally moderate in degree. From the material studied, no conclusion can be drawn as to the relationship between radiosensitivity of the tumor and vascular damage.

8. A single biopsy, taken between the seventh and eleventh day during a course of fractionated irradiation, will yield considerable information concerning the radiosensitivity of the tumor and the effectiveness of the irradiation technic.

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SUMARIO

**Alteraciones Histológicas Producidas en el Carcinoma Céluloescamoso de la Boca y Orofaringe por la Irradiación Externa Fraccionada con Rayos X**

Para estudiar las alteraciones histológicas observadas en el carcinoma escamocelular de la boca y orofaringe así como ciertos problemas afines relacionados con los efectos de la radiación, obtuviéronse a varios plazos, por medio de biopsias, ejemplares de 28 enfermos que se hallaban en tratamiento.

A 24 de los enfermos se les trató con una técnica tipo, recibiendo 400 r diarios a la piel (dosis diaria de 275 r al tumor) hasta una dosis total de 6,000 a 6,500 r por tumor en 23 a 28 días. En los otros 4 enfermos se utilizó una técnica experimental, que consistió en la administración de una llamada "dosis diaria inadecuada," a saber, 200 r a la piel (dosis diaria de 135 r al tumor), o sea la mitad del tratamiento tipo, pero continuándola aproximadamente el doble de tiempo, obteniendo así una dosis total comparable. Los factores físicos de la terapéutica fueron: 200 kv. 0.5 ó 2.0 mm. de filtro de cobre; 20 ma.; 50 cm. de distancia foco-piel; dos portales laterales en el cuello, 10 × 15 cm. (a veces 8 × 10 cm.); capa de hemirreducción 0.9 ó 1.8 mm. de cobre; 10 a 40 r por minuto.

Llegóse a las siguientes conclusiones:

1. El efecto destructor de la radiación sobre el carcinoma escamocelular de la boca y orofaringe se obtiene con varios procesos: muerte aguda de las células, hiperplasia progresiva de las células hasta convertirse en células neoplásicas gigantescas y queratogenia irradiatoria.

2. La muerte aguda de las células es la alteración más común, afectando por igual el citoplasma, el núcleo y otros componentes celulares y soliendo observarse en los primeros siete días. Este es el proceso con el cual se destruyen las células más radiosensibles y cuya importancia no ha sido suficientemente recalcada.

3. Las células menos sensibles, que no experimentan una muerte aguda, se agrandan progresivamente hasta convertirse en células cancerosas gigantescas. Esto se realiza mediante dos mecanismos distintos: (1) inflación y vacuolación del citoplasma y en menor grado del núcleo, probablemente por virtud de un trastorno físico-químico del intercambio inter- e intracelular de líquidos; y (2) perturbación de la función nuclear, dando por resultado la formación de varias anomalías nucleares.

4. La queratogénesis irradiatoria, otro mecanismo de destrucción celular, representa la aceleración, bien en velocidad o intensidad, del proceso normal de queratinización, siendo un fenómeno citoplásmico.

5. La subirradiación de un tumor (principalmente en forma de una dosis

diaria ineficientemente pequeña) produce alguna destrucción de las células cancerosas, pero principalmente provoca maduración de las células más radiorresistentes.

6. La alteración más pronunciada en el estroma consiste en fibrosis de sustitución, secundaria y proporcional a la destrucción irradiatoria de un tumor. La irradiación también acrecienta la hialinización del estroma del tejido conjuntivo, y en menor grado, produce en el interior de algunos fibroblastos, alteraciones degenerativas, a saber, inflación y vacuolación.

7. Con la irradiación fraccionada, el daño experimentado por los vasos sanguíneos suele ser leve, y a veces moderado. Del material estudiado, no puede sacarse conclusión alguna acerca de la relación entre la radiosensibilidad del tumor y la lesión vascular.

8. Una sola biopsia, ejecutada entre el séptimo y el undécimo día de una tanda de irradiación fraccionada, facilitará considerable información con respecto a la radiosensibilidad del tumor y la efectividad de la técnica irradiatoria.

# Suppurative Bronchopneumonia with Cavitation[1]

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DURING THE WINTER and spring of 1944–45, the authors saw approximately 3,500 cases of pneumonia at a naval hospital. In this group there were 7 cases of a rather bizarre type of bronchopneumonia characterized by parenchymal suppuration and necrosis with cavity formation. Because this entity is not particularly well known and the pertinent radiologic literature is sparse, these cases will be reported in some detail.

Although several fragmentary references had been made to the pathology of this disease in the continental literature (1, 2, 4, 6, 10, 11, 21, 28), no adequate description of the clinical and roentgen findings was recorded prior to Kessel's report, in 1930 (9). That investigator noted the clinical and roentgen aspects of 5 cases in detail and appended a gross and microscopic description of 3 additional cases which came to necropsy. In general, credit for a proper understanding of this disease must go to the Mt. Sinai Thoracic Group, whose investigations have led to a clear concept of the pathogenesis of suppurative bronchopneumonia (16, 17, 18, 19, 20, 27, 29).

## INCIDENCE

The incidence of suppurative bronchopneumonia in our series was 0.2 per cent (7 cases in a group of 3,500 pneumonias). That this lesion is not a rarity is well demonstrated by the fact that the Mt. Sinai group was able to accumulate a series of 120 cases during a period of ten years (18). Many cases, particularly the milder ones, are probably overlooked because of a general unfamiliarity with the lesion.

The Mt. Sinai investigators reported an equal incidence in the sexes and an occurrence in all age groups. There seems, however, to be a preponderant frequency in children and young adults.

## ETIOLOGY

The bacteriology of necrosuppurative bronchopneumonia as determined in our cases is based upon cultures of the sputum obtained prior to the institution of chemotherapy. In 4 cases, a pure culture of B-hemolytic streptococcus was found. In the remaining 3 cases, no abnormal pathogens could be cultured. The explanation for the presence of the B-hemolytic streptococcus may lie in the fact that many of the cases of pneumonia followed in the wake of an epidemic of scarlet fever. Other investigators have incriminated *Staphylococcus aureus*, *Pneumococcus*, and *Streptococcus viridans* as well as the B-hemolytic streptococcus as causative organisms (18). In almost all of the cases reported in the literature, a pure culture of the offending organisms has been found in the pus or necrotic lung tissue, in contradistinction to the mixed infections present in anaerobic lung abscesses.

## PATHOLOGY

In the few cases which have come to autopsy, the lesions, either single or multiple, consisted of a bronchopneumonia with varying degrees of suppuration and

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necrosis. The infection usually involved one or more bronchopulmonary segments, with extension to the pleura. Gross abscess formation was noted with coalescence of suppurative areas of destroyed alveolar septa and bronchi. Two types of bronchopneumonia with abscess formation occur: the type in which focal necrosis is secondary to a predominantly suppurative pneumonic lesion and the type in which the abscess formation is foremost and the surrounding pneumonitis is minimal.

Microscopically, the areas of suppuration are diffuse throughout the involved segment of lung. The alveoli and bronchioles are distended with pus. The explanation for the necrosis is twofold, lying first in the suppurative process itself and, second, in inflammatory vascular lesions resulting in thrombosis and anemic infarction. The latter process is well described in Kessel's original contribution (9).

## CLINICAL FEATURES

The clinical symptoms of suppurative bronchopneumonia are fever, cough, and the expectoration of purulent sputum. Frequently, there is a history of an antecedent upper respiratory tract infection. Pleuritic pain is common. The disease most often occurs in young healthy individuals.

There are no characteristic physical findings. The signs are those of any bronchopneumonic infiltration and are often insignificant compared with the lesion seen on the roentgen film. Because of the pneumonitis, physical signs of cavitation are frequently not detectable. Nor is there anything characteristic about the blood count. Most commonly, there is a moderate leukocytosis, but this is not always present. In the more protracted cases, a secondary anemia may be noted.

From the clinical point of view, the cases may be grouped into four varieties.

1. The first group comprises those cases in which the clinical course and laboratory findings are those of an ordinary bronchopneumonia, except for the roentgen demonstration of cavitation. Most of these cases have an uncomplicated recovery.

2. The second group includes the more severe, protracted cases which tend to spread to new bronchopulmonary segments. Some of the patients go on to spontaneous recovery after weeks or months of prolonged relapsing illness. In others chronic bronchiectasis develops, secondary to the pulmonary suppuration and superimposed atelectasis with its resultant interstitial fibrosis.

3. The third group consists of the cases with local surgical complications.

(*a*) *Aerobic pulmonary abscess:* This is an infrequent complication of suppurative bronchopneumonia. In the typical case, the abscess is unilocular, solitary, superficially located, with adherence of the overlying pleura. The cavity contains a varying amount of pus and air, depending on the degree of patency of the communicating bronchus or bronchi.

(*b*) *Pleural involvement with empyema or pyopneumothorax:* The abscess may rupture into the pleural space, resulting in either a localized or diffuse empyema. Air in the pleural space may or may not be demonstrable on the roentgen film. The absence of air may be due to compression of the perforation by the empyema fluid.

4. The fourth group includes those cases in which general or regional spread has occurred.

(*a*) *Cerebral involvement* is a rare complication of the severe form of the disease and is characterized by either a suppurative meningitis or cerebral abscess formation.

(*b*) Rarely, diffuse *septic embolic phenomena* with metastatic abscess formation may take place secondary to the pulmonary suppuration and its associated septic thrombophlebitis.

(*c*) *Mediastinitis and pericarditis* may occasionally occur as direct extensions from the pulmonary lesions.

## ROENTGEN CHARACTERISTICS

Because of the paucity and the nonspecificity of the clinical symptoms and

signs, the diagnosis of suppurative bronchopneumonia depends primarily upon the roentgen findings. The cardinal feature is the presence of one or more areas of cavitation within an area of pneumonic consolidation. The bronchopneumonic infiltration may be multiple or confined to one bronchopulmonary segment. There may be some difficulty in distinguishing the areas of cavitation from irregular areas of radioparency due to a resolving pneumonia. However, the early appearance of the cavitation in the course of the disease, its sharply defined borders, and an air fluid level (when the latter is present) usually make differentiation possible. In doubtful cases, laminagraphy may be of considerable value.

The cavity may be single *ab initio* or may result from the coalescence of several smaller cavities. The cavities may rapidly diminish in size and disappear. This is probably due to closure of the communicating bronchus. On the other hand, a rapid increase in the size of the cavity may take place in the face of resolution of the surrounding pneumonic infiltration. Simultaneously, the outline of the cavity may become circular and more sharply defined. In all likelihood, this is due to partial occlusion of the communicating bronchus by inflammatory exudate, producing a ball-valve effect. These tension cavities may persist for long periods of time, and have undoubtedly been mistaken for congenital pneumatoceles. In the absence of cavitation, there is no one roentgen sign which is pathognomonic of suppurative bronchopneumonia. However, Rabin believes that the presence of atelectasis and emphysema, due to bronchial obstruction by inflammatory exudate, should suggest that the pneumonia is of the suppurative variety. Furthermore, he feels that slow resolution should raise a similar suspicion (20).

The solitary abscess cavity or the multiple areas of cavitation may rupture into the pleural space, resulting in a localized or diffuse empyema or pyopneumothorax. This frequently obscures the underlying pulmonary lesion. Roentgen differentiation of a pyopneumothorax from an unperforated lung abscess may sometimes be difficult or even impossible. Neuhof and Touroff (19) mention two roentgen features which are suggestive of pyopneumothorax: (*a*) The fluid level frequently extends to the thoracic cage, with no intervening lung. (*b*) Roentgenoscopically the fluid level is usually more mobile than in pulmonary abscess.

### DIFFERENTIAL DIAGNOSIS

The diagnosis of suppurative bronchopneumonia can usually be made from a combination of the clinical and roentgen findings. However, the more severe forms may require differentiation from other disease, *e.g.*, pulmonary tuberculosis, putrid lung abscess, bronchogenic carcinoma, actinomycosis, and atypical (virus) pneumonia. Tuberculosis can be excluded by repeated smears and cultures of the sputum. If the latter is scanty, bronchoscopic aspiration may be necessary. Similarly, bronchoscopy may be invaluable in the differential diagnosis of bronchogenic carcinoma. In the rare case of putrid lung abscess with a blocked bronchus, there may be no foul sputum. The diagnosis may then be in abeyance until the appearance of a foul sputum or a putrid empyema.

The irregular mottled appearance of an atypical (virus) pneumonia may simulate suppurative bronchopneumonia. However, the leukopenia, the absence of purulent sputum, and the subsequent roentgen course of the disease should make the correct diagnosis apparent.

Rare suppurative lesions such as actinomycosis can be properly differentiated only after repeated bacteriologic study of the sputum.

### TREATMENT

In the first two clinical groups, *i.e.*, pulmonary abscess incidental to extensive necrosuppurative bronchopneumonia and pulmonary abscess as the predominant factor with a surrounding necrosuppurative

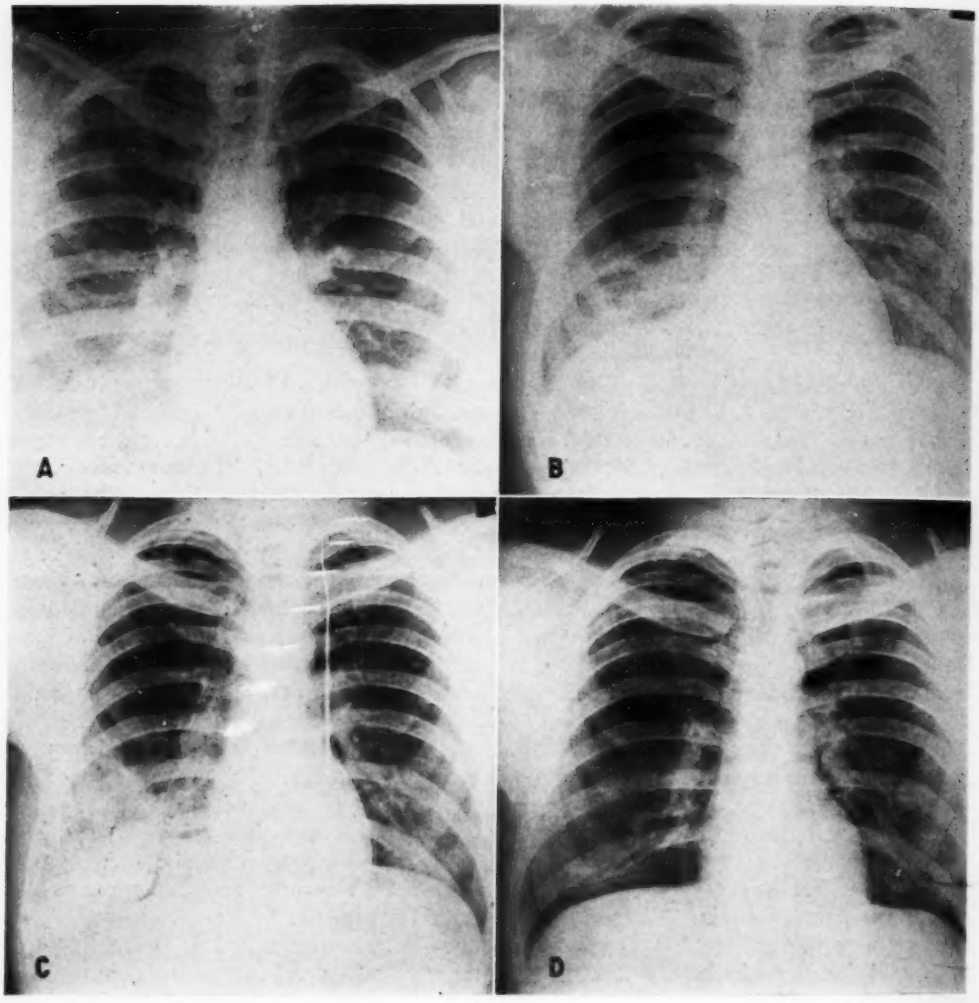


Fig. 1. Case 1. A. At onset of pneumonia: lesion in right lower lobe; no cavitation. B. Six days after onset: area of cavitation has appeared. C. Twenty-one days after onset: cavitation persists. D. Two months after onset: lung clear.

pneumonic infiltration, surgical intervention is not necessary (18, 19). The disease usually resolves spontaneously; less frequently it eventuates in bronchiectasis. The pulmonary and pleural complications, however, require surgical management. The true encapsulated aputrid lung abscess surrounded by a narrow reaction zone of inflammatory tissue is the only pulmonary lesion for which operative treatment may be indicated. Neuhof and Touroff (19) state that there is no operative mortality, little postoperative morbidity, and a complete cure in the latter type of case. On the other hand, imminence of or actual perforation into the pleural cavity is a real indication for surgical intervention. Similarly the regional extensions into the mediastinum and pericardium and the metastatic abscesses require surgical drainage, but the prognosis in these complications is grave.

Although our series of cases is small, there is good evidence to suggest that

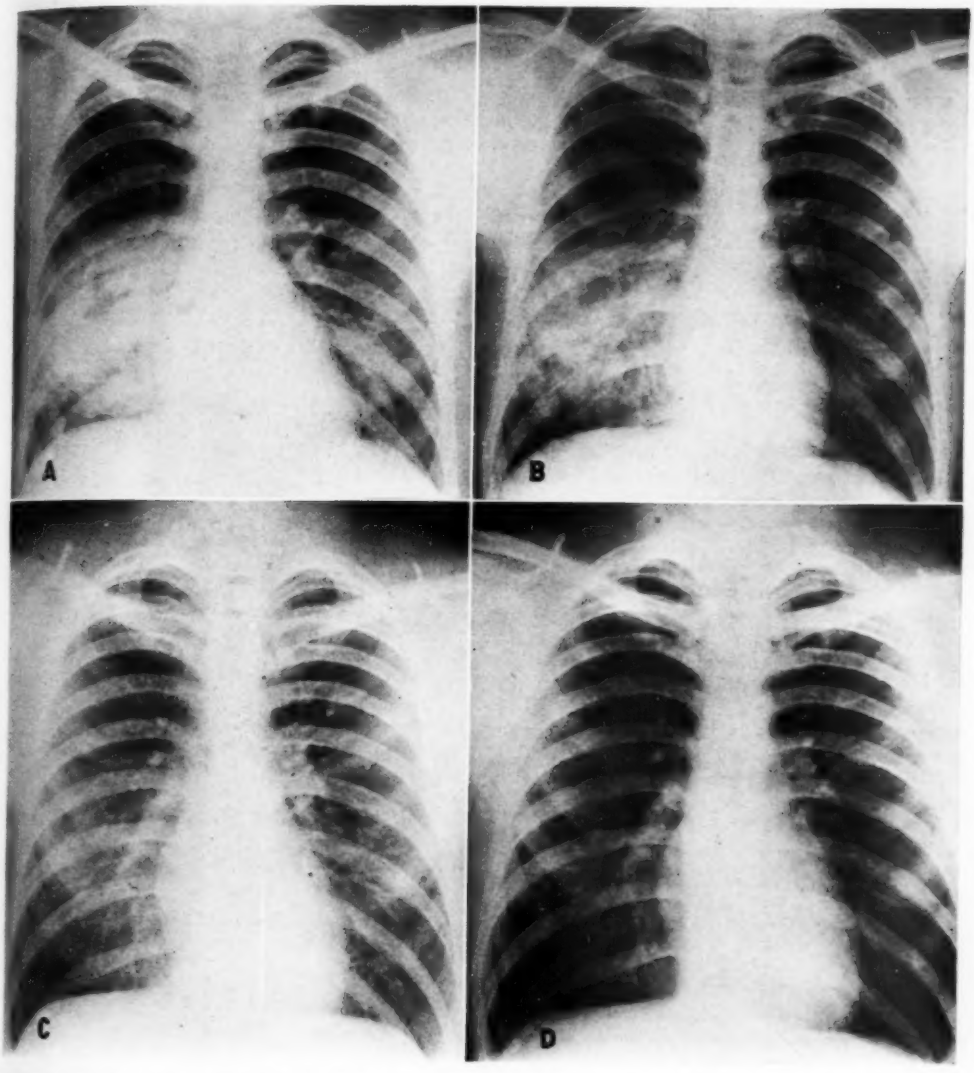


Fig. 2. Case 2. A. At onset of pneumonia: area of cavitation in center of right lower lobe lesion. B. Five days after onset: considerable decrease in lesion; cavity somewhat smaller. C. One month after onset: almost complete clearing. D. Six weeks after onset: lungs clear.

penicillin is of definite value in the treatment of this disease. The use of penicillin has resulted in a marked reduction in toxicity and has probably served to prevent the occurrence of the more serious complications.

## CASE REPORTS

CASE 1: A. D., 18-year-old apprentice seaman, was admitted to the hospital on April 9, 1945, with a diagnosis of acute coryza. Unfortunately his clinical record was misplaced, so that only fragmentary information is available.

*Laboratory Examinations:* Sputum culture on April 24 yielded only normal pharyngeal organisms. On April 25, a blood culture showed no growth.

*Roentgenograms of the Chest:* On April 10, an area of pneumonic infiltration in the supradiaphragmatic portion of the right lower lung field was noted. Re-examination on April 24 showed suggestive evidence of cavitation, which was confirmed. Further study, May 1, demonstrated some resolution of the pneumonitis but persistence of the cavity. On

May 10, further resolution of the pneumonitis was noted and also some diminution in the size of the cavity. The latter was almost entirely gone by May 16. On June 19, repeat roentgen study showed only a slightly increased prominence of the bronchovascular trunk markings at the site of the lesion but no evidence of cavitation. Bronchoscopy was performed on July 12 and a normal bronchial mucosa was found. Lipiodol was instilled and no evidence of bronchiectasis could be found. The patient was discharged to duty, well, on Aug. 2, 1945.

CASE 2: T. G., 18-year-old apprentice seaman, was admitted to the hospital on June 11, 1945, with a diagnosis of possible bronchopneumonia.

*History:* The past history was irrelevant. A week before admission, the patient reported to the local naval dispensary complaining of sore throat, fever, and cough. Although originally non-productive, the cough soon became productive of a mucopurulent sputum. There had been no chest pain, dyspnea, or hemoptysis.

*Physical Examination:* The temperature on admission was 99.4° F., the pulse rate 88 per minute, and the respirations 20 per minute. There were no positive physical findings except for slight injection of the pharynx.

*Laboratory Examinations:* The red blood count was 4,390,000 cells per cubic millimeter. The white blood count was 13,400, with 65 per cent segmented polymorphonuclear leukocytes, 2 per cent non-segmented polymorphonuclear leukocytes, 28 per cent lymphocytes, and 5 per cent monocytes.

*Roentgenogram of the Chest:* A chest film showed an area of pneumonic consolidation occupying the right middle lobe area, with an irregular radiolucent cavity in the superior portion of the lesion. There were also flocculent pneumonic infiltrations along the trunks to the left base.

*Course:* Four grams of sulfadiazine were given immediately, followed by 1.0 gm. every four hours. This was discontinued on June 12, at which time penicillin therapy was started in a dosage of 15,000 units intramuscularly every three hours. The dose was reduced to 10,000 units every three hours June 18, and the drug was discontinued completely on June 20. On June 14, the patient was considerably improved. His temperature was normal but he was raising a moderate amount of yellow mucoid sputum which was not foul in odor. Re-examination of the chest, June 16, showed further resolution of the pneumonic process in the right mid lung field. The areas of cavitation were still demonstrable but their borders were much less distinct. There was almost complete resolution of the pneumonia in the left lower lobe at this time. There was, however, an afternoon elevation of temperature to 100–101° F. By June 21, the patient was afebrile and had only occasional cough, productive of a very scanty sputum. On July 2, further resolution was noted on the roentgen film. Re-examination of the chest on July 11 showed complete resolution of the pneumonic process with no residual evidence of cavitation. The patient was discharged to duty, well, on July 30.

CASE 3: H. R., 18-year-old apprentice seaman, was admitted to the hospital on June 23, 1945, with a diagnosis of scarlet fever.

*History:* The past history was irrelevant. Two days before admission, the patient had a sore throat. The following day he noticed a diffuse rash over his body and a cough productive of a thick, tenacious sputum.

*Physical Examination:* The temperature on admission was 103.6° F., the pulse rate 130 per minute, and the respirations 26 per minute. The pertinent physical findings were marked reddening of the pharynx, a strawberry tongue, bilateral cervical adenopathy, and a typical scarlatina rash.

*Laboratory Examinations:* Throat cultures failed to demonstrate any evidence of B-hemolytic streptococcus. Only the normal pharyngeal organisms were obtained.

*Course:* Penicillin, 20,000 units every three hours, was given intramuscularly. The temperature dropped to normal in the next several days and the drug was discontinued on June 28. At that time, the patient was asymptomatic. On July 3, his temperature rose to 102° F., and he began to complain of pain in the right side of the chest. Roentgen examination of the chest at this time showed an area of pneumonic consolidation at the right base, with a central zone of rarefaction. Penicillin was again started, in the same dosage as before, and the temperature abruptly fell to 99° F. the next morning. The penicillin was discontinued on July 4 because of marked urticaria. Roentgen examination of the chest on July 11 showed considerable resolution.

On July 12, the temperature again rose to 104° F., and the patient complained of a cough productive of mucoid sputum. Some fine râles over the right mid-lung field posteriorly were noted at this time. Sulfadiazine, 1.0 gm. three times a day, was started on July 13. The next day the patient felt much better. By July 16, his temperature had returned to normal and he was asymptomatic. Sulfadiazine was discontinued on July 19. On July 23, re-examination of the chest showed further resolution of the pneumonic process. Repeat roentgen study on Aug. 6 showed both lung fields clear. The patient was discharged to duty, well, on Aug. 21.

CASE 4: H. R., 17-year-old apprentice seaman, was admitted to the hospital on May 26, 1945, with a diagnosis of pneumonia of the left lower lobe.

*History:* The past history was non-contributory. For two weeks prior to admission the patient complained of chills, fever, malaise, weakness, and a cough productive of a tenacious, purulent sputum, which was blood-streaked on one occasion. On the morning of admission, sharp pain developed in the left chest, aggravated by breathing or coughing.

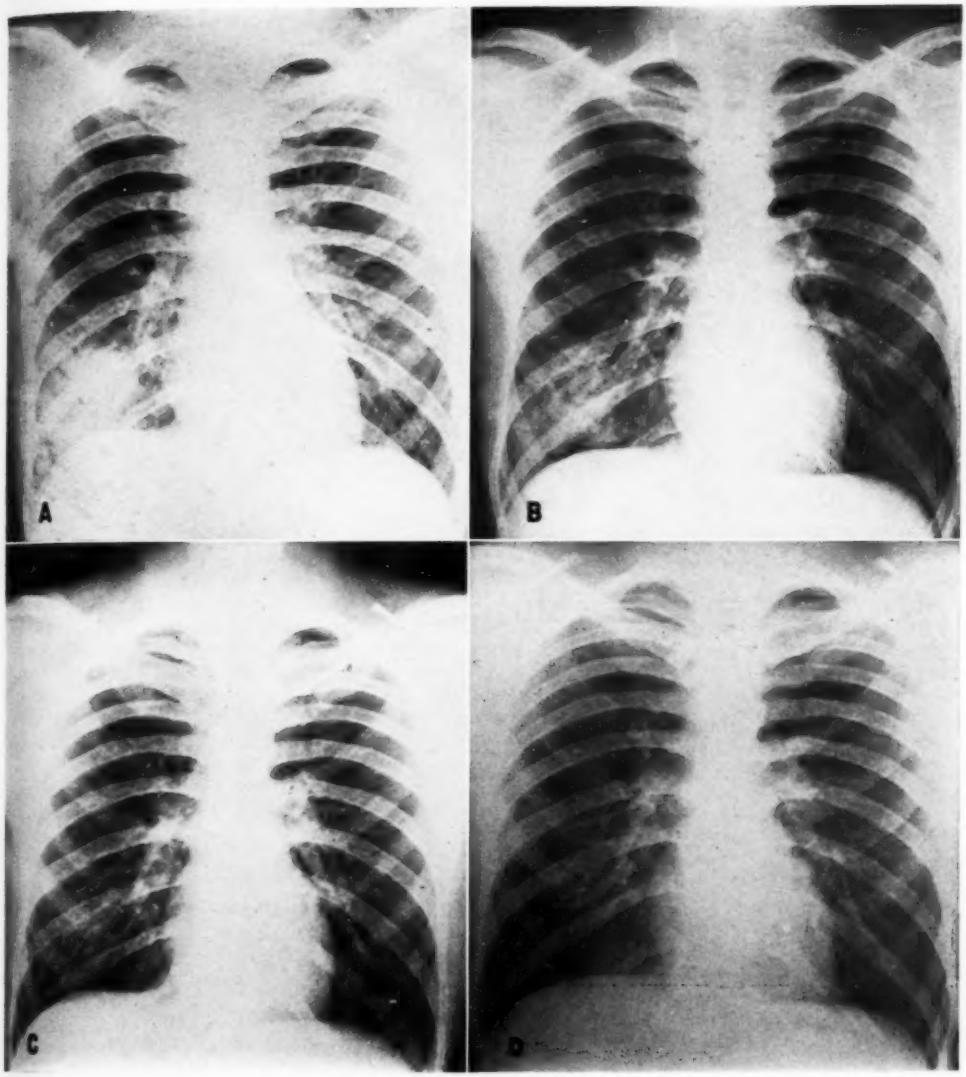


Fig. 3. Case 3. A. At onset of pneumonia: lesion in right lower lobe, with several small areas of cavitation. B. Eight days after onset: lesion resolving; few small areas of cavitation remaining. C. Twenty days after onset: almost complete resolution. D. Thirty-three days after onset: lungs clear.

*Physical Examination:* The temperature on admission was 105.4° F., the pulse rate 112 per minute, and the respirations 50 per minute. The important physical findings were an inflamed pharynx, bilateral cervical adenopathy, and dullness, diminished expansion and breath sounds over the left lower lobe posteriorly. A faint friction rub was heard at the level of the ninth left rib in the mid-axillary line.

*Laboratory Examinations:* The red blood count was 4,000,000 cells per cubic millimeter, with 11.5 gm. hemoglobin. The white blood count was 28,450, with 73 per cent segmented polymorphonuclear leukocytes, 18 per cent non-segmented polymorphonuclear leukoctytes, and 9 per cent lymphocytes. Cultures of the sputum yielded a pure growth of B-hemolytic streptococcus and no tubercle bacilli.

*Roentgenogram of the Chest:* On May 26, a chest film showed small patches of pneumonic infiltration along the trunks to both bases, more marked on the right side.

*Course:* The patient was placed in an oxygen

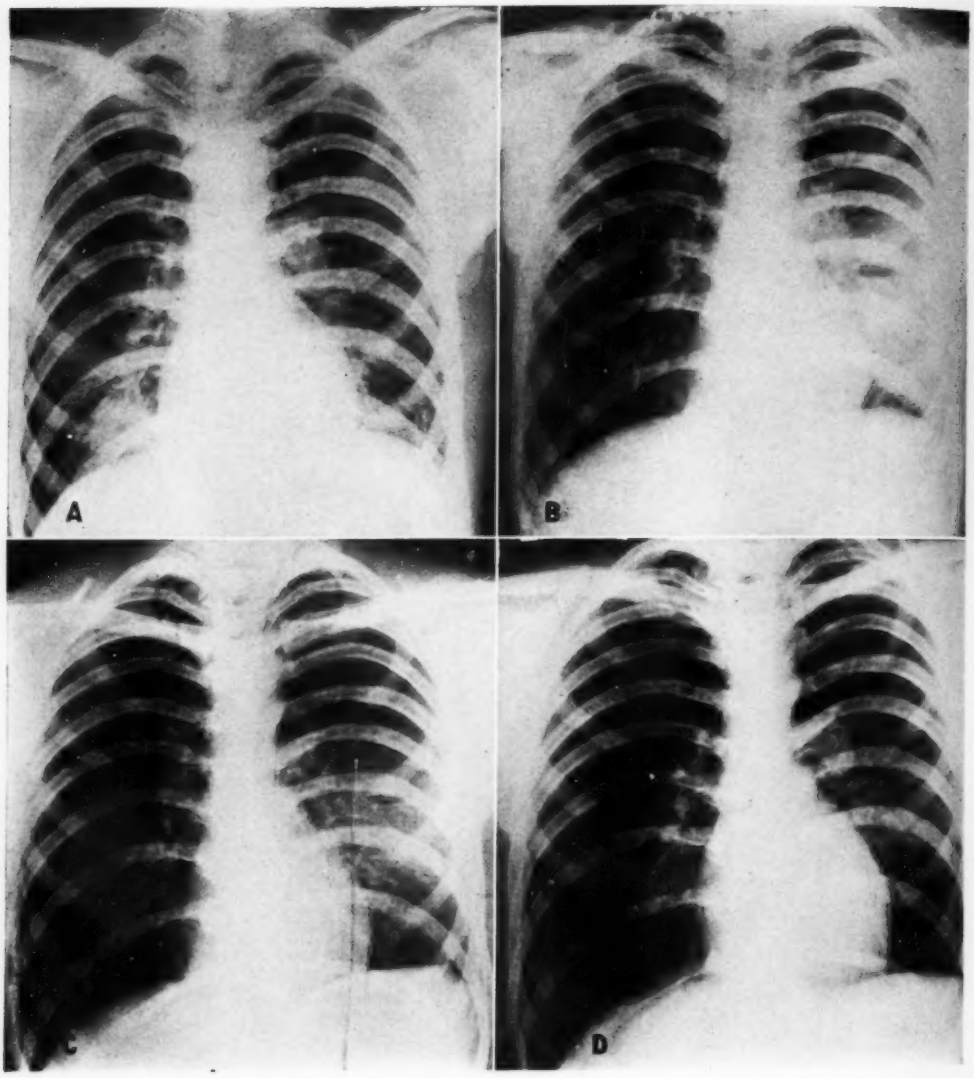


Fig. 4. Case 4. A. At onset of pneumonia: lesions along trunks to both bases, more marked on right. B. Twelve days after onset: right lower lobe clear; extension of process in left lower lobe, with area of cavitation in upper part of lesion. C. One month after onset: considerable clearing of lesion, with persistence of small cavity. D. Ten weeks after onset: both lungs clear.

tent, and 30,000 units of penicillin were given intramuscularly every three hours. The temperature fell to 99° F., by crisis, overnight. The following day, however, it rose to 103° F., and physical signs of fluid in the left pleural cavity appeared. A thoracentesis was performed, and 75 c.c. of slightly cloudy, thin, yellow fluid was removed. Direct smear showed a few polymorphonuclear leukocytes but no organisms. There was no growth on culture. Roentgen examination of the chest following thoracentesis disclosed some resolution of the pneumonic process in the right lower lobe and an effusion in the left pleural cavity.

On June 6, thoracentesis of the left pleural cavity was again performed but only 25 c.c. of fluid was obtained. Direct smear at this time showed numerous polymorphonuclear leukocytes and a few gram-positive diplococci. Again there was no growth on culture. On June 7, two abscess cavities were noted in the left lower lobe. Penicillin was

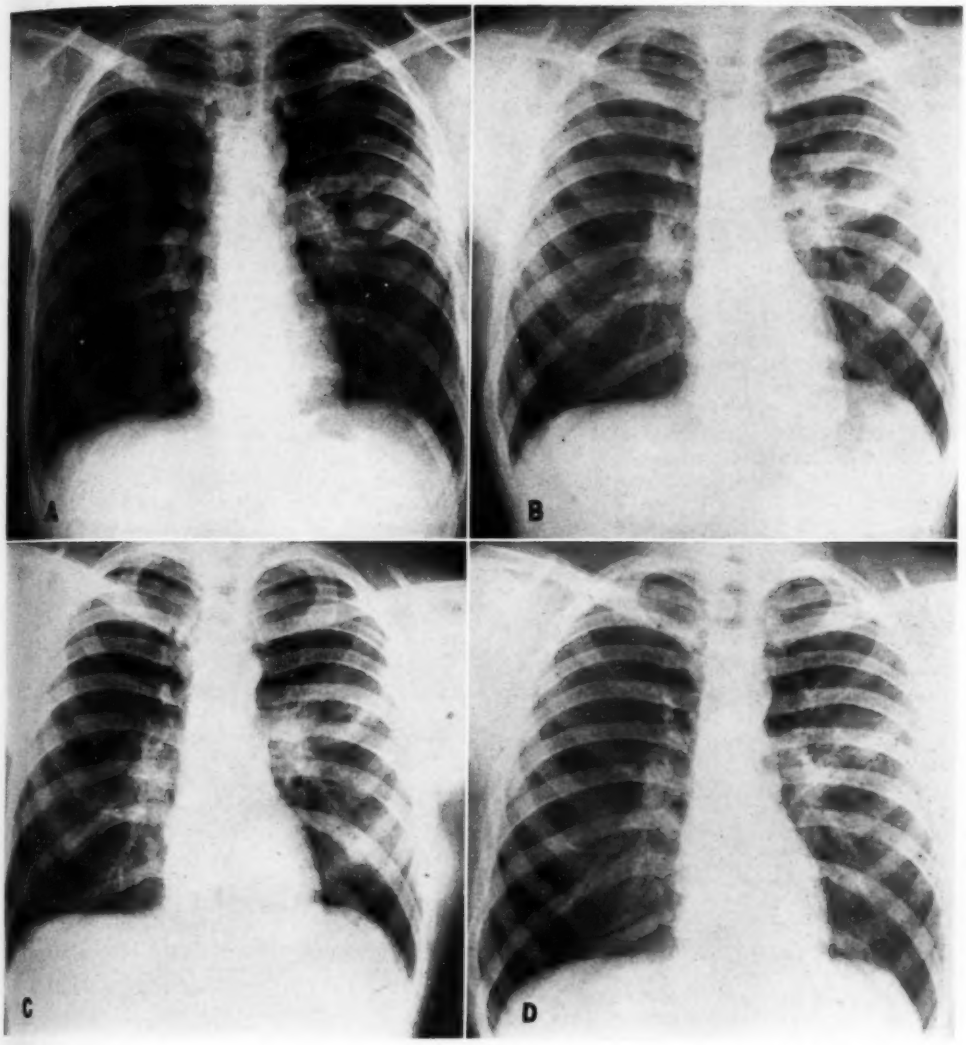


Fig. 5. Case 5. A. At onset of pneumonia: area of pneumonia in lower part of left upper lobe, with a large irregular area of cavitation. B. Fourteen days after onset: considerable resolution of lesion, with some reduction in size of cavity. C. Twenty-four days after onset: further resolution, with persistence of small area of cavitation. D. Thirty-seven days after onset: lungs clear.

discontinued on June 9 because of the occurence of severe urticaria.

By June 19, the temperature returned to normal and remained so thereafter. Physical examination on this date showed diminished expansion of the left side of the chest and signs of pleural thickening. The patient was clinically well except for a slight cough productive of a small amount of sputum. On June 26, repeat roentgen examination revealed considerable absorption of the fluid in the left pleural cavity. Some residual pleural thickening and elevation of the left dome of the diaphragm were noted. The abscess cavity was definitely smaller in size.

By July 9 there was complete disappearance of the abscess cavity, and re-examination on July 26 demonstrated only a slight degree of pleural thickening in the left lower lobe. On August 6 the vital capacity was 3.5 liters. By Aug. 23, it had increased to 4 liters. At the latter time, chest expansion was normal bilaterally, and only minimal pleural thickening in the left costophrenic angle could be demonstrated on the roentgen film. The patient was discharged to duty, well, on Aug. 27.

CASE 5: D. H., 17-year-old apprentice seaman, was admitted to the hospital on Feb. 19, 1945. He had been taking 1.0 gm. of sulfadiazine daily for five weeks up until Feb. 14, as part of the Navy prophylactic campaign against respiratory infections in recruits.

*History:* The past history was irrelevant. Five days prior to admission, the patient had a sore throat, fever, and a cough, productive of large quantities of mucopurulent, blood-tinged sputum. On Feb. 19, he first noticed sharp pleuritic pain over the left lower chest and a diffuse rash over his body.

*Physical Examination:* The temperature on admission was 104.4° F., the pulse rate 108 per minute, and the respirations 20 per minute. The essential physical findings were a typical scarlatina rash, considerable injection of the pharynx, bilateral anterior cervical adenopathy, and dullness and coarse râles over the left lower lobe posteriorly.

*Laboratory Examinations:* The white blood count was 19,350, with 81 per cent segmented polymorphonuclear leukocytes, 13 per cent non-segmented polymorphonuclear leukocytes, 4 per cent lymphocytes, and 2 per cent monocytes. Throat culture showed a pure growth of B-hemolytic streptococcus.

*Course:* The patient was given 20,000 units of penicillin intramuscularly every three hours. The temperature returned to normal on Feb. 25, and penicillin was discontinued on March 1. Roentgen examination of the chest, March 5, showed an area of pneumonic consolidation with cavitation in the superior division of the left lower lobe. Direct smears of the sputum showed many polymorphonuclear leukocytes and numerous gram-positive cocci in short chains. No acid-fast bacilli could be found. On March 10 the patient was clinically well and not raising any sputum. Re-examination of the chest at this time revealed some diminution in the size of the cavity and the surrounding pneumonitis. On March 13, treatment with sulfadiazine was started, 1.0 gm. three times a day. This regime was continued until April 1. On March 20, there was further reduction in the size of the abscess cavity. On March 23, cultures of the sputum yielded a pure strain of B-hemolytic streptococcus. No tubercle bacilli could be found. Re-examination of the chest showed almost complete resolution of the abscess cavity but considerable pneumonitis still remained.

On March 27, treatment with penicillin was reinstituted, with a dose of 20,000 units intramuscularly every three hours. This was discontinued on April 4, at which time the patient was clinically well except for occasional non-productive cough. On April 12, repeat roentgen examination of the chest showed complete resolution of the abscess cavity with only a slight prominence of the bronchovascular trunk markings in the affected area.

On June 14, bronchoscopy was done, revealing a moderate degree of inflammation of the tracheobronchial mucosa, with a small amount of mucopurulent exudate. At the same time lipiodol was instilled and a normal arborization pattern of the tracheobronchial tree was demonstrated. The patient was discharged to duty, well, on June 19.

CASE 6: M.P., 17-year-old seaman, second class, was admitted to the hospital on Jan. 28, 1945, with a diagnosis of scarlet fever.

*History:* The past history was non-contributory. Approximately five days before admission the patient had a sore throat, followed two days later by a diffuse rash over his entire body. The day prior to admission, he began to have a slight nonproductive cough. There was no chest pain or dyspnea.

*Physical Examination:* The temperature on admission was 102° F., the pulse rate 96 per minute, and the respiratory rate 24 per minute. The relevant findings on physical examination were an inflamed pharynx, bilateral anterior cervical adenopathy, and a typical scarlatina rash.

*Laboratory Examinations:* The red blood count was 4,000,000 cells per cubic millimeter with 14 gm. of hemoglobin. The white blood count was 9,000 with 77 per cent segmented polymorphonuclear leukocytes, 12 per cent non-segmented polymorphonuclear leukocytes, and 11 per cent lymphocytes.

*Course:* On Feb. 6, some dullness and crepitant râles were noted over the right lower lobe. The patient was placed on a regime of 1.0 gm. of sulfadiazine every four hours. Roentgen examination of the chest on Feb. 7 showed an area of pneumonic infiltration in the dorsal segment of the right lower lobe with cavity formation and an air-fluid level. By Feb. 10, the temperature had gradually returned to normal and the patient felt considerably better. Re-examination of the chest on Feb. 13 showed a reduction in the extent and density of the pneumonic involvement but the abscess cavity appeared unchanged. On Feb. 9, culture of the throat yielded a pure growth of B-hemolytic streptococcus. A similar organism was found in the sputum. Numerous smears and cultures of the sputum failed to demonstrate any evidence of tubercle bacilli. On Feb. 22, chemotherapy was discontinued and roentgen examination of the chest showed further resolution of the pneumonic process with a reduction in the size of the cavity. The tuberculin skin test at this time was negative.

On March 3, the temperature rose to 100° F., and roentgen examination revealed an increase in the extent of the pneumonitis around the abscess cavity and also an increase in the size of the cavity. No further chemotherapy was given, and the temperature slowly returned to normal by March 7. On March 19, re-examination of the chest showed almost complete disappearance of the abscess cavity. Further roentgen study on April 2 showed no evidence of cavitation and only a slight thickening of the bronchovascular trunk markings in this region. On May 19, the chest was completely clear.

Bronchoscopy was performed on June 14. Mod-

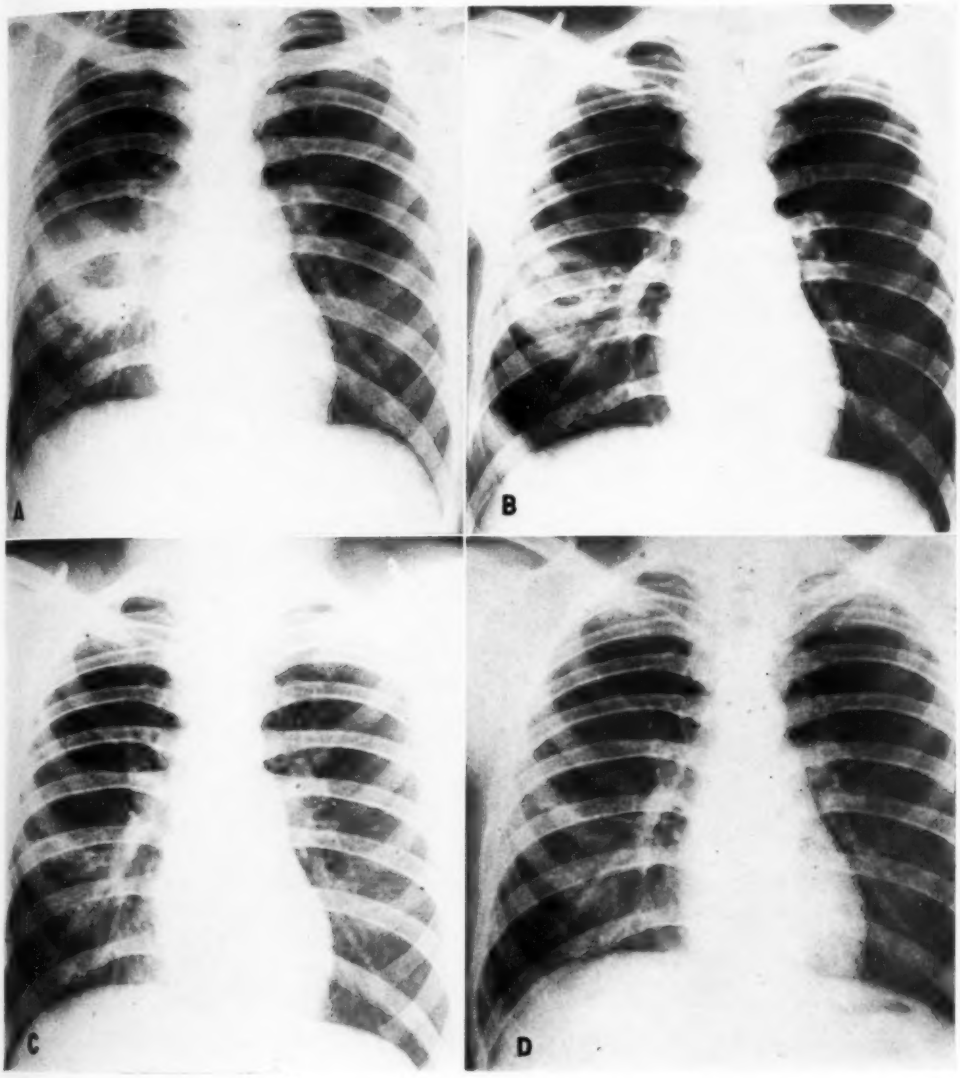


Fig. 6. Case 6. A. At onset of pneumonia: lesion in upper part of right lower lobe, with fairly large area of cavitation. B. One month following onset: primary cavity has disappeared, and a second one has appeared slightly lateral to the first. C. Six weeks after onset: almost complete resolution. D. Three months after onset: lungs clear.

erate injection of the tracheobronchial tree, with a small amount of mucopurulent exudate in both main bronchi, was noted. At the same time lipiodol was instilled and a normal bronchial tree was demonstrated. The patient was discharged to duty, well, on June 6.

CASE 7: S. S., 18-year-old apprentice seaman, was admitted to the hospital on April 22, 1945, with a diagnosis of bronchopneumonia.

*History:* The past history was irrelevant except for a cerebral concussion from an automobile accident in childhood. For two days prior to admission, the patient had been hospitalized at a local naval dispensary because of fever, chills, dyspnea, dizziness, and slight stiffness of the neck. He also had malaise, anorexia, one episode of vomiting, and a cough productive of mucopurulent sputum.

*Physical Examination:* The temperature on admission was 103.6° F., the pulse rate 100 per minute, and the respiratory rate 20 Pertinent physical findings were injection of the posterior pharynx and a few crepitant râles at the right base posteriorly.

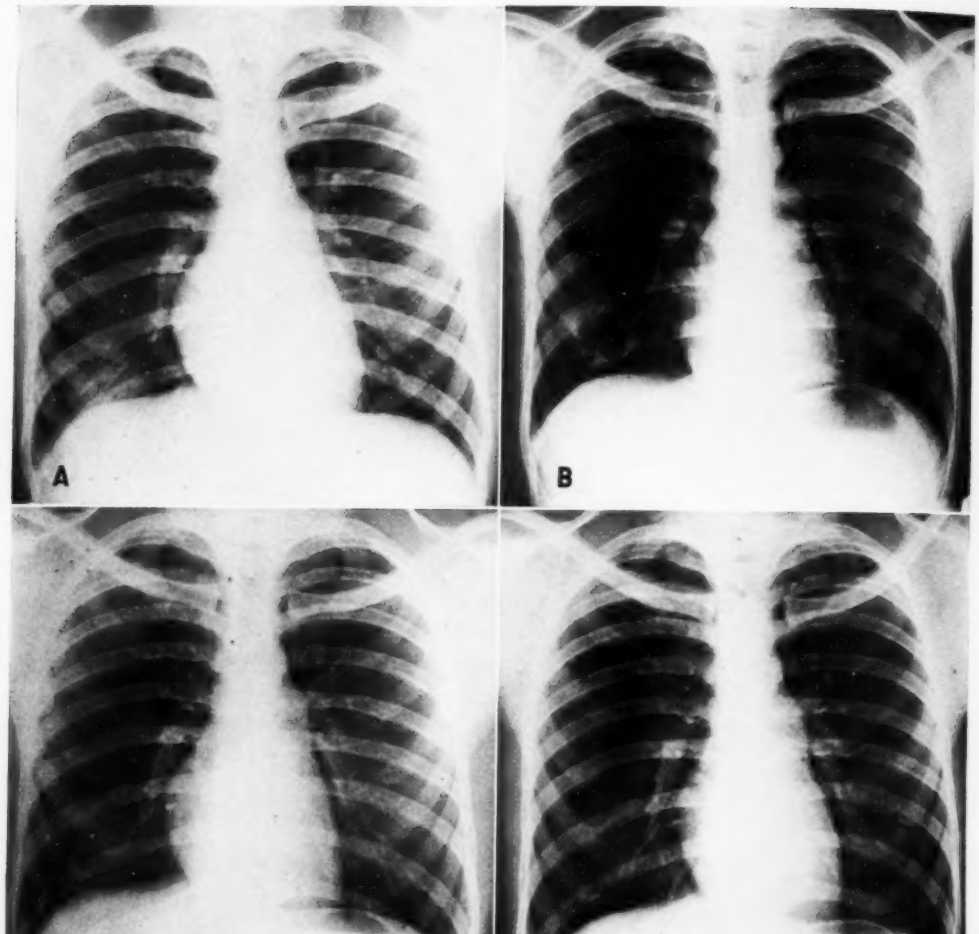


Fig. 7. Case 7. A. At onset of pneumonia: small lesion in right lower lobe. B. Nine days after onset: large thin-walled area of cavitation in right lower lobe. C. Fourteen days after onset: marked reduction in size of cavity. D. Thirty-seven days after onset: lung clear.

*Laboratory Examinations:* The red blood cells numbered 5,230,000 per cubic millimeter, with 15 gm. of hemoglobin. The white blood count was 16,550, with 61 per cent segmented polymorphonuclear leukocytes, 22 per cent non-segmented polymorphonuclears, 15 per cent lymphocytes, 2 per cent monocytes. The blood culture showed no growth, but culture of the sputum yielded a pure strain of B-hemolytic streptococcus. Repeated smears and cultures were negative for tubercle bacilli.

*Roentgenogram of the Chest:* On April 22, a small area of pneumonic consolidation was seen immediately above the right dome of the diaphragm. The remainder of both lung fields was clear.

*Course:* Penicillin therapy was immediately begun, with a dose of 15,000 units intramuscularly every three hours. The temperature fell to 99° F. overnight by crisis and remained normal thereafter. On April 30, penicillin was discontinued, after a total of 1,100,000 units had been administered. At this time, the patient had been afebrile for three days but was still raising some clear mucoid sputum.

On May 1, repeat roentgen examination of the chest revealed an oval cavity measuring 3 × 5 cm. in the right lower lobe. On May 16, there was a considerable reduction in the size of the cavity. Further roentgen study on June 19 demonstrated almost complete disappearance of the lesion, with

only slight residual prominence of the bronchovascular trunk markings in the right lower lobe. On July 7, there was complete clearing.

On July 12, bronchoscopy was done and showed a normal tracheobronchial mucosa. At the same time, lipiodol was instilled and a normal arborization pattern of the bronchial tree was demonstrated. The patient was discharged to duty, well, on July 24.

## SUMMARY

1. The incidence, etiology, pathology, and clinical features of necrosuppurative bronchopneumonia are described, and the clinical varieties are noted.

2. The typical roentgen characteristics are presented. Cavitation within an area of pneumonia is pathognomonic of this form of pneumonia. However, atelectasis and emphysema in an area of pneumonitis and slow resolution should also suggest that the pneumonia is of the suppurative type.

3. A brief review of the complications, differential diagnosis and treatment is appended.

4. Seven cases are reported in some detail.

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## SUMARIO

### Bronconeumonía Supurada con Cavitación

Entre 3,500 casos de neumonía observados en un hospital naval, encontráronse 7 de bronconeumonía caracterizada por supuración parenquimática y esfacelo con

formación de cavernas Las características clínicas comprendieron tos, fiebre, esputo purulento y dolor pleurítico. Los signos físicos y los hallazgos de laboratorio no fueron típicos.

Reconócense cuatro grupos clínicos de la enfermedad mencionada: (1) casos que parecen de bronconeumonía ordinaria salvo por el cuadro roentgenológico de cavernas; (2) casos más graves y prolongados, con tendencia a la propagación a nuevos segmentos broncopulmonares; (3) casos complicados con absceso pulmonar aerobio o invasión pleural con empiema o pioneumotórax; y (4) casos con difusión general o regional.

La característica radiográfica cardinal consiste en la presencia de una o más zonas de cavitación en una zona de hepatización neumónica. Las cavernas pueden disminuir de tamaño y desaparecer o agrandar rápidamente en presencia de resolución de la infiltración neumónica circundante.

Las formas simples de la enfermedad suelen resolverse espontáneamente. Las complicaciones pueden exigir la intervención cruenta. En la pequeña serie comunicada, la penicilina pareció ser de valor.

Sumarízanse las siete historias clínicas. En todas se despejaron los pulmones, y en ningún caso se necesitó la cirugía.

# Roentgen Findings in Functional Disturbances of the Gastro-Intestinal Tract[1]

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FUNCTIONAL derangement of the gastro-intestinal tract has recently received more attention from the radiologist. Reviewing the literature and looking back on the experience of recent years, one is struck by the way in which this emphasis has varied. In the early days of the use of the barium meal, the functional and the organic abnormalities were probably considered of equal importance. Indeed, the changes in function were sometimes used as indirect evidence of a lesion, even though definite organic change could not be demonstrated. The pendulum seemed to swing toward the other extreme for a time, and one gained the impression that the various functional disorders were being, for the most part, ignored in gastro-intestinal diagnosis. Now, however, we appear to be approaching a more neutral position and function is again being stressed. We therefore propose to review some of the highlights in the physiology of the gastro-intestinal tract that should be of interest to the roentgenologist in his routine work. Then, considering each segment of the alimentary canal, we will attempt, when possible, to correlate functional derangements with organic pathologic processes.

## ESOPHAGUS

*Normal Physiology:* Normal deglutition is dependent upon the combined, co-ordinated efforts of the pharynx and esophagus. The initial phase is voluntary, with the tongue carrying a food bolus into the pharynx. Almost immediately the pharynx and larynx are elevated, the upper passages close off, and the pharyngeal musculature contracts, driving the bolus past a relaxed cricopharyngeal ring into the esophagus. Here the muscular activity continues as the primary peristaltic wave. Although the exact pharyngeal mechanism is still debated, it certainly comprises a set of closely co-ordinated involuntary reflex acts that end in the primary peristaltic wave which, together with gravity, acts as the downward propelling force. During quiet respiration, the esophageal opening is closed off, presumably by the tonic contraction of the cricopharyngeus muscles.

Three types of muscular activity occur in the esophagus. The primary waves originate with the pharyngeal contraction. Secondary waves are thought to result from local mechanical stimulation and are also seen in obstructive lesions of the lower esophagus. They act as true peristaltic waves and will travel in both directions. During sustained inspiration, peristaltic waves may terminate in the so-called phrenic ampulla—actually a ballooning out of the terminal esophagus with a narrow contraction ring just above (Fig. 1, A). If inspiration is prolonged, material in the ampulla will regurgitate for a short distance. The anatomical basis for the narrowing is not well established, but a pinchcock action of the diaphragm during deep inspiration may perhaps account for the apparently normal ampulla formation. The so-called tertiary contractions occur most frequently in patients past middle age. They appear to be simultaneous contraction rings, varying in degree and frequency but giving the esophagus a peculiar serrated appearance. They are usually momentary, disappearing almost as rapidly as they appear. The contractions may be so marked as to give the esophagus a "corkscrew" appearance. Beading and temporary multiple diverticula-like pock-

[1] Read, by invitation, at the Annual Meeting of the Medical Society of New Jersey, April 23, 1947. Accepted for publication in June 1947.

ets may occur. "Curling" is another descriptive term given to these tertiary contractions (Fig. 1). Schatzki (12), at one time, suspected paraesophageal adhesions as the underlying cause. Others believe there is a disturbance in innervation or actual bulging of weakened portions of the esophageal wall. The condition is almost entirely asymptomatic, and Templeton (13) believes it to be relatively insignificant.

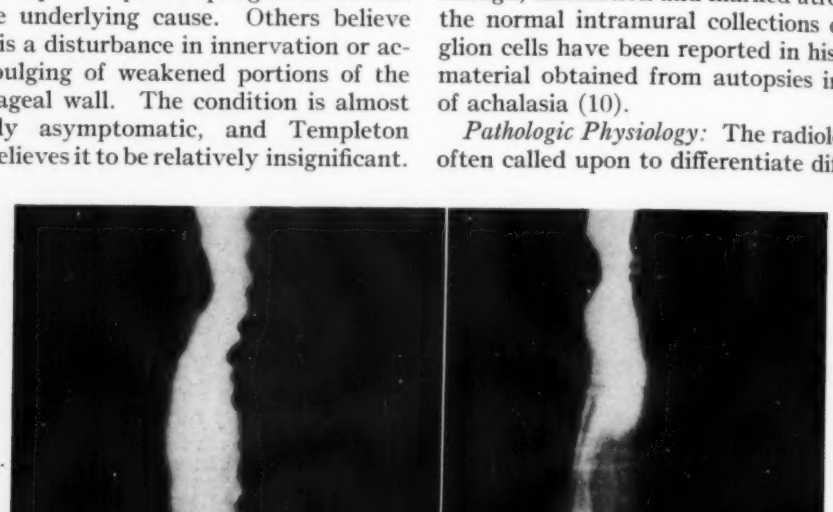


Fig. 1. A. Barium-filled esophagus showing phrenic ampulla and curling phenomenon.
B. Same esophagus a moment later. The "curling" pattern has disappeared.

The problem of the cardiac sphincter has caused some controversy. Anatomically a thickened muscular ring does not exist but, physiologically, active sphincteric action is present. The tonic muscular contraction of the esophagus at the cardia is quite likely an expression of gastric tone and probably parallels it. A pinchcock action of the diaphragm at the hiatus may be partly responsible; however, fluoroscopy of patients with a hiatus hernia will usually demonstrate active and competent sphincteric action with the support of the diaphragm lacking. The exact innervation has not been worked out, but the autonomic nervous system seems to play an active role. Interestingly enough, dissolution and marked atrophy of the normal intramural collections of ganglion cells have been reported in histologic material obtained from autopsies in cases of achalasia (10).

*Pathologic Physiology:* The radiologist is often called upon to differentiate difficulty in swallowing caused by a central neurologic lesion from that due to a local cause. Inflammation, neoplasm, and obstruction due to a foreign body are the chief organic lesions to be ruled out. These being absent, we can conclude that the difficulty in starting the act of deglutition probably has its origin in the central nervous system, or in some primary myopathy.

If and when the normal co-ordinated mechanism of deglutition is upset, pharyngeal diverticula may result (Fig. 2). These are little outpouchings at the site where the constrictor muscles leave a weak spot

in the posterior wall of the esophageal introitus. The diverticulum may just be beginning to show when one sees a patient with some vague difficulty in swallowing. When these diverticula become large they cease to fall into the realm of the functional and become organic lesions, which usually require surgical repair.

We are not convinced that the secondary peristalsis described above is purely an expression of normal function, since we have often seen something of this nature in cases of minor obstruction. Areas of spasm may be observed associated with the trauma of a foreign body, where a rather diffuse wave begins at the site of the lesion, spreading out both caudad and cephalad, to give a diffuse narrowing not unlike that described by others as secondary peristalsis. We have also seen this in what was thought to be a subacute or acute esophagitis and in areas where a foreign body has apparently scratched or actually lodged in the wall of the esophagus, with resultant spasm.

Whether or not there actually is a sphincter which fails to relax in achalasia, bears some discussion. The fact that no long-standing areas of spasm occur at any other spot than the lower end argues in favor of its presence. We have, furthermore, seen cardiospasm occur in the short-esophagus type of diaphragmatic hernia, where the pinch-cock action of the diaphragm could not possibly have been the mechanism producing the obstruction. It is our opinion that minor degrees of cardiospasm occur more often than is thought, being too transient to cause any continued dilatation or symptomatology.

In the marked irritability accompanying esophagitis, it has been our impression that the curling phenomenon is apparently increased. Indeed, we have come to the conclusion that the presence of curling as described by Schatzki and others is definitely a pathologic finding and rarely occurs without some superimposed irritability of the esophagus, for in our experience it is not outstanding unless there is an underlying pathologic process.

Fig. 2. Film of the upper esophagus showing a small pharyngeal diverticulum, non-obstructing.

## STOMACH

*Normal Physiology:* The empty stomach is tonically contracted and exhibits periods of muscular activity called "hunger contractions." The gastric wall is capable of considerable tonal change allowing for active accommodation to varying food volumes. Peristaltic waves, on the average of three per minute, start as shallow ripples near the cardia, grow deeper and stronger as they advance, and run through the antrum to the pylorus or end in what appears to be a systolic contraction of the antrum. The antrum has been observed contracting rhythmically with the duodenum. Alvarez (1) suggests the presence of gastric pacemakers, one in the gastric wall near the cardia, the other on the proximal side of the pyloric antrum.

The modern tendency in the problem of gastric emptying is to minimize the importance of a pyloric sphincter and to stress variations in intragastric pressure subsequent to general tonus changes in the gastric wall. Fat in the duodenum inhibits gastric activity through the humoral

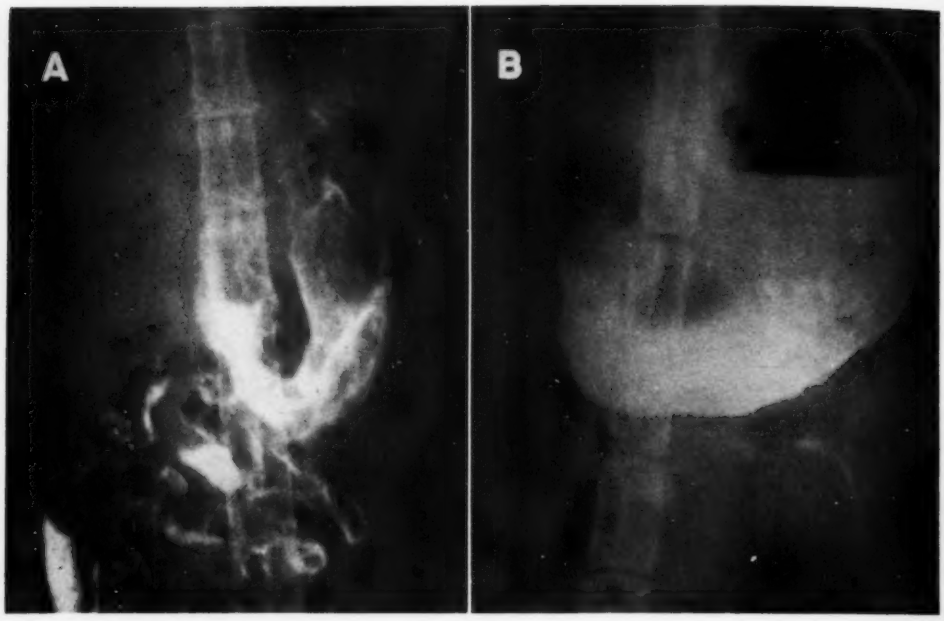


Fig. 3. A. The barium-filled stomach and upper intestines of a cat, one hour and forty-five minutes after the ingestion of a barium and water mixture under average normal conditions. B. Same stomach after a dose of ephedrine. Note dilatation, relaxation, and atonicity, with "apparent pylorospasm." The time interval is the same. Over-stimulation of the sympathetics has caused a marked delay in emptying time.

medium of enterogastrone, a hormone-like substance produced in the duodenal wall. Acids and other irritating substances in the duodenum inhibit gastric motility reflexly through the vagus. Distention of the duodenum with chyme has the same effect, and there appears to be a definite balance between intragastric and intraduodenal pressures. Foods in fluid state pass rapidly through the pylorus; solids are held back until properly macerated. Stimuli from within the gastric lumen seem to have some regulatory effect upon the tone of both the pyloric antrum and the sphincter. The vagus and sympathetic innervation is a regulatory mechanism, the first predominating. Sympathetic stimulation is mainly inhibitory, while vagus stimulation increases gastric activity; thus actually a mixture of responses may occur. Vagotomy in man is followed by a period of depressed motor activity and muscular hypotonicity; later the peripheral intrinsic mechanism "takes over," giving almost normal function, with perhaps some delay in the initial emptying time.

*Pathologic Physiology:* The subject of antral spasm and pylorospasm in the presence of local, adjacent, or distant disease is one that has provoked much discussion. It is perhaps the most frequently observed alteration in the gastro-intestinal motility gradient. Templeton does not believe there is sufficient experimental or clinical evidence to prove the presence of so-called "reflex pylorospasm" from other intra-abdominal diseases. He found no increased incidence of pylorospasm in patients with evidence of biliary, appendiceal, or renal disease. Since delayed emptying not caused by a local organic lesion appears to be an expression of gastric hypomotility and hypotonicity, it sometimes gives rise to a roentgen picture which suggests that the pylorus is in spasm, although it may actually not be so. We are inclined to agree with Templeton on the basis of the evidence he presents and on the basis of

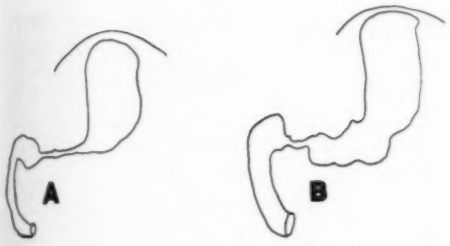


Fig. 4. A. Small antral ulcer producing diffuse antral spasm. B. Same stomach after three weeks of dietary regime. The antral spasm has for the most part relaxed. An associated neoplasm was suspected at the first examination. (Tracings of x-ray films.)

(Figs. 4 and 5). At first sight, however, we are often confronted by a stubborn and difficult problem when attempting to rule out neoplasm in this region.

Earlier in the history of the use of the barium meal, there were some observers, notably Carman, who would ascribe the various functional abnormalities to a definite underlying local cause. Observations prove this an unreliable deduction. The error has been that diagnoses of peptic ulcer were made when there was no obvious local lesion. The diagnoses were made on

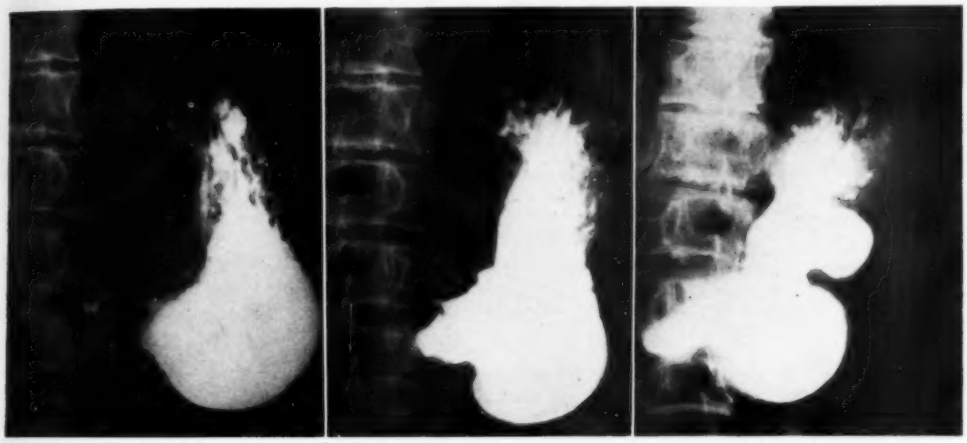

Fig. 5. Stomach films showing an antral spasm associated with an ulcer on the lesser curvature and one in the duodenum as well. The films show various phases of contraction and relaxation.

some unpublished experimental evidence of our own. Nevertheless, it is this appearance, whatever the cause may be, that all of us have been calling "pylorospasm" (Fig. 3). This picture is often seen apparently secondary to gallbladder disease and other remote intra-abdominal causes producing six-hour retention. A twenty-four-hour barium meal retention rarely, if ever, occurs.

If an ulcer is found in the first part of the duodenum or in the actual pyloric channel, true pylorospasm is very common. With actual local ulcerative antral gastritis, as described by Golden (7) the secondary nature of the antral spasm and pylorospasm is actually proved by a change following conservative treatment the basis of secondary signs only, even when a crater could not be seen. Moreover, emphasis was laid on the reflex effect of distant lesions on the stomach. Carman (5), for example, listed ten probable causes for what he called gastrospasm and spoke of the primary and secondary functional diagnostic findings. He stressed the indirect signs of duodenal ulcer, namely, the alterations in tone, peristalsis, and motility of the stomach. We now know that the functional irregularities, though not to be disregarded, should be considered due to local disease only when a definite organic lesion can be shown.

Emotional states can bring on exactly the same findings. In this regard, it is of interest to watch an apparent "pyloro-

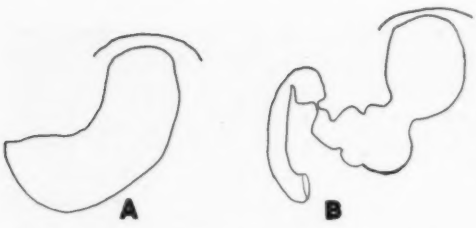


Fig. 6. A. Tracing of a stomach immediately after administration of barium, showing "apparent pylorospasm." B. Same stomach a few moments later, after discussion of food with the patient.

spasm" relax and the stomach regain its tone and activity under the fluoroscope when one mentions food to a patient (Fig. 6). This change will occur in an otherwise orthotonic stomach which seems to have rebelled at the intrusion of anything as unsavory and unpalatable as a barium and water mixture. The autonomic control of the stomach activity had probably been affected either through the sympathetics or the vagus or both.

### DUODENUM

*Normal Physiology:* Duodenal movements are varied and independent of the stomach. X-ray observation reveals considerable duodenal activity. The duodenal bulb may remain distended at intervals or contract immediately and empty. Sometimes normal individuals show apparent irritability and the bulb fills but partially. This is followed, after a short rest, by a more normal activity with decreased duodenal tonus. Peristaltic waves and sleeve-like contractions may affect the cap in a rhythmic manner or indeed involve the entire duodenum. Many contraction waves die out in the lower part of the descending limb or near the beginning of the ascending limb. When this occurs, the barium column just ahead will partially regurgitate, but this is not a true antiperistalsis. Apparently, the portion of the duodenal wall in relation with the superior mesenteric artery fails to relax completely with the oncoming peristaltic wave and produces a more or less normal physiologic obstruction. Investigators have felt that the superior mesenteric artery causes an actual organic obstruction (6). However, an indentation of the duodenal loop is almost never demonstrated. Once barium passes this point, be it a point of pressure or a hypertonic focus, it readily continues on to the jejunum. Sometimes the regurgitated barium will balloon out the duodenal cap or pass through a relaxed pylorus into the stomach. On occasion, true antiperistalsis is seen in the normal duodenum.

*Pathologic Physiology:* Most of us are familiar with the disturbed duodenal physiology which occurs with or without anorexia nervosa. Only now and again do we see this condition associated with definite organic abnormality. A true anorexia nervosa may often lead to such a marked degree of voluntary starvation that a vicious cycle develops; that is to say, the loss of weight may allow an increased drag of the mesenteric root and its vessels over the distal portion of the duodenum and thereby produce an actual organic obstruction. In such a case, reverse peristalsis, which is a normal finding in the duodenum, may become increased and result in stasis and shuttling of the barium back and forth within the duodenal loop.

### JEJUNUM AND ILEUM

*Normal Physiology:* The normal movements of the small bowel mix the chyme with digestive juices, facilitate absorption, and force the unwanted remnants into the large bowel. In general, there are two types of activity. One is essentially myogenic, appearing as constantly changing rhythmic segmental contractions. These have a mixing and kneading effect, but there is no real displacement of the intestinal contents. The so-called pendular movements affecting larger segments are a variant of this myogenic activity. Secondly, there are peristaltic waves which are dependent on the integrity of the myenteric plexus, through which the waves are co-ordinated. Bayliss and Starling (3) in their original work described peristalsis as a wave of contraction preceded by a wave of inhibition. In more recent years, Raiford and Mulinos (11) recorded con-

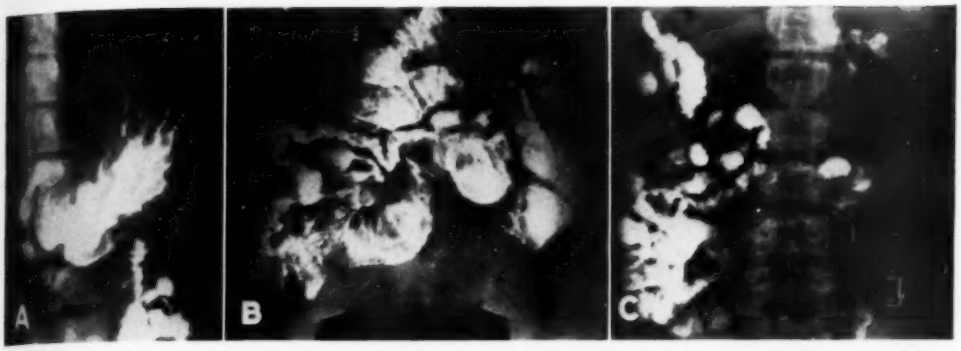


Fig. 7. A. Stomach of a patient with a diffuse inflammatory process in the wall, showing little other than diffuse thickening of the mucosal contours. B. Barium-filled small bowel (mid portion). At operation only the mesentery was involved. There are delayed motility and moderate dilatation. C. Barium in the lower small bowel after having passed through the abnormal portion in B. The caliber of the bowel is normal.

tractions of the circular and longitudinal muscles of the exteriorized colon of the dog. They found that "stimuli" applied to the mucosa are followed by contractions of the longitudinal muscle at and below the stimulus, and by contraction of the circular muscle above. Atropine and cocaine will abolish peristalsis while myogenic contractions continue. Dilatation is a part of the myenteric reflex and is not due to inhibition. Whatever the mechanisms, they are most certainly inherent in the gut wall and not dependent upon an extrinsic nervous mechanism.

Alvarez's (1) gradient theory is interesting and offers a way of explaining the apparent inherent polarity of the small bowel. He suggests there are downward gradations in all forms of physiologic activity in the bowel wall from the duodenum to the ileocecal junction, and that these gradations are responsible for the orderly progress of digestion. Influences altering or reversing the gradient result in abnormal function and subjective symptoms.

The extrinsic nervous mechanism consisting of vagal and sympathetic innervations seems to have a regulatory effect. For the most part, vagal stimulation results in increased muscular tone and activity, which is expressed through Auerbach's myenteric plexus. The sympathetic is mainly inhibitory as far as the main muscular tunic is concerned. Stimulation of Meissner's submucous plexus through the sympathetic fibers results in active secretion of mucus and vigorous contractions of groups of intestinal villi.

The chemical mediator theory helps to explain the effects of nerve stimulation. An epinephrine-like substance liberated at the endings of the sympathetics has excitatory as well as inhibitory components. Acetylcholine seems to be the excitor substance liberated at the parasympathetic endings. It is deactivated by specific and non-specific tissue esterases. The relative amounts of the mediator substances produced during any one period due to reflex or central nervous system influences may account for the many variations which seem to exist in so-called "normal activity." Bargen (2) in a recent paper says it seems futile to designate a so-called normal for the transit time of intestinal contents. The transit time of the small intestines in one apparently normal person may be less than an hour while in another it is as much as five hours. It is, therefore, probably advisable to speak in terms of average transit time and a broad zone of normal. Bargen suggests that a particularly fruitful field for research exists in the nervous control of the intestines. It is interesting to note that vagotomy and splanchnicectomy have little lasting effect on the digestive functions in man (1).

The ileocecal sphincter permits interval

Fig. 8. A. Normal small bowel pattern, one hour after ingestion of barium meal.

passage of intestinal contents and hinders reflux into the ileum. An actual thickening of the circular muscle fibers forms a sphincter guard for the orifice. Observations in man reveal that during digestion the sphincter opens rhythmically. During emotional excitement or subsequent to the act of swallowing, the frequency of the openings increases. The increased muscular activity at the sphincter during digestion possibly helps to explain why barium enemas frequently fail to show a reflux into the ileum in patients who have had breakfast on the morning of the examination. We therefore make it mandatory for the patient to omit breakfast, particularly when we are interested in the terminal ileum.

*Pathologic Physiology:* Various disturbances in the motility gradient of the small intestine are seen in extra-alimentary tract disease. The patient with reflex motor disturbances of the stomach may also show a hypermotility and/or multiple spastic areas in the gut. Retroperitoneal pathology may cause various degrees of reflex ileus. Spastic manifestations result from mesenteric disease, such as calcifying mesenteric nodes and from less chronic processes (Fig. 7).

Fig. 8. B. Small bowel shown in Fig. 8, A, at same time interval, showing so-called "milk reaction." Note multiple spastic areas and segmentation.

C. Same small bowel at same interval after withdrawal of the milk allergen.

There is usually a functional derange-

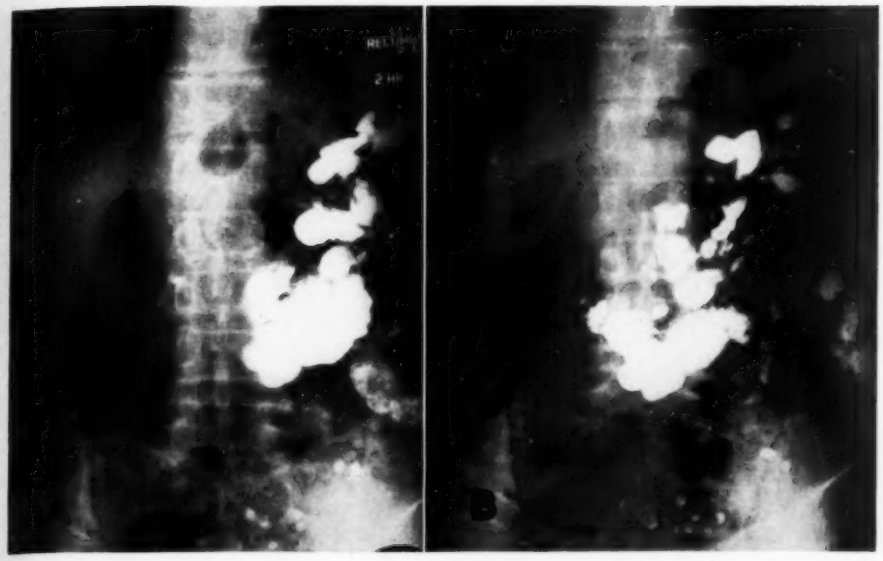

Fig. 9. A. Small bowel film showing marked hypomotility, clumping, and smoothing of the mucosal folds in a case of hypoproteinemia with edema of the bowel wall (two-hour film). B. Six-hour film showing little further progress of the barium in four hours. Barium in the large bowel is residual from previous barium enema.

ment of the small gut when the mesentery is involved by a neoplasm. The bowel pattern may be unusually abnormal in such a case without any actual organic change taking place. Lymphosarcoma may cause such a disturbed intestinal pattern. Spasm, segmentation, and disturbed motility result. Other lesions in the mesentery have been shown to be responsible for the same type of change, however, the only difference being that there was not such a large area of involvement. Carcinoma spreading from elsewhere in the gut and certain benign tumors which ostensibly block the lymphatics or affect the nerve supply to the bowel can also be responsible. Golden (8) quotes Vespignani as showing similar changes in what he described as sclerosing mesenteritis.

Psychic functional disturbances may often be confused with organic processes. All sorts of gastrocolic, gastroenteric, and enterocolic reflexes may result. Golden cites the effect of fright on the small bowel pattern of laboratory animals. He shows some interesting patterns, both before and after such an effect was produced (8).

Food allergy, sensitivity, or idiosyncrasy may produce striking changes in motility and pattern. In its early stages hypermotility without any change in the bowel pattern is the usual finding, but later in the disease more marked changes in motility and pattern supervene. There often is a gastric retention accompanying hypermotility of the bowel. Segmentation and hypomotility may be a still later manifestation (Fig. 8, A, B, C).

The patterns of abnormal nutrition (deficiency or irritation pattern) (Fig. 9) may at first be purely functional. Organic changes are, as Golden and others have shown, a late manifestation (Fig. 9).

So-called acute non-specific catarrhal enteritis will at times show definite small bowel functional disturbances which in a severe stage might be confused with organic disease (Fig. 10).

## COLON

*Normal Physiology:* The movements of the colon, though varied, do bear similarity to those seen in the small bowel, but there are longer periods of relative inactivity.

Fig. 10. A gastro-intestinal film showing a simultaneous filling of the stomach, small bowel, and proximal colon in a patient with extreme hypermotility (one-hour film). The patient was suffering from an acute gastro-enteritis following apparent "food poisoning." He had eaten some shellfish the previous day, to which he considered himself sensitive.

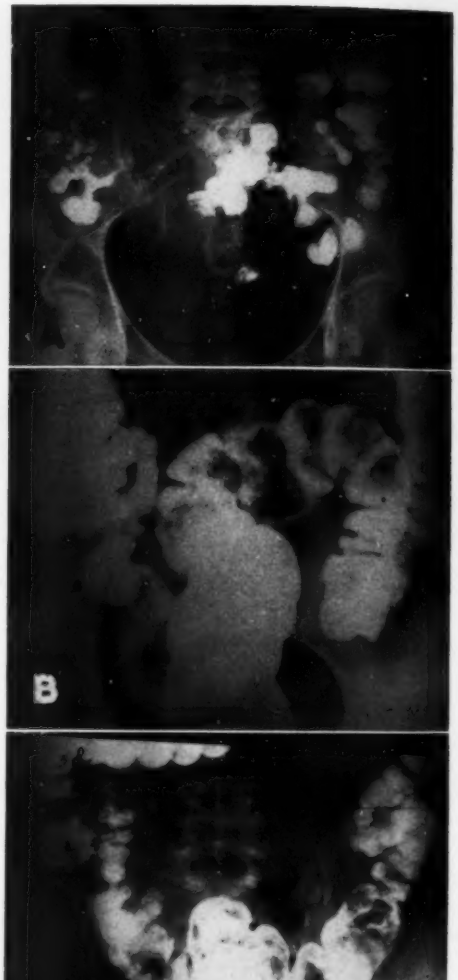


Fig. 11. A. Scybala shown in the gas-filled rectum in a patient with severe constipation. B. Barium enema showing fecal masses in an atonic dilated sigmoid. C. Same case as B, post-evacuation. In spite of the stimulus of distention by the enema, there are still scybala in both sigmoid and rectum.

Haustral formation seems to be dependent upon contractions of the muscularis mucosae and shortening of the taeniae coli. The slow but constantly changing haustrations have a mixing and kneading effect upon colonic contents. Mass movements of the large bowel usually occur several times a day and most frequently are stimulated through the mechanism of the gastrocolic reflex set off by food entering the stomach. The taste, smell, or thought of food, disturbing emotions, and other psychic stimuli may reflexly initiate the movements. The rushes, usually beginning near the hepatic flexure, carry the fecal contents all the way to the pelvic colon. The descending colon is relatively empty except during the mass movements.

Defecation is the final purpose of the large bowel. The rectum is normally empty except during and prior to defecation. The defecation reflex occurs when intrarectal pressures reach 40 to 50 mm. of mercury (4). Fecal material may pass the narrowed rectosigmoid junction at the tail end of a mass movement or there may be just a plain overflow from the pelvic colon. Thereafter strong peristaltic waves are accompanied by contraction of the abdominal musculature and the diaphragm, and

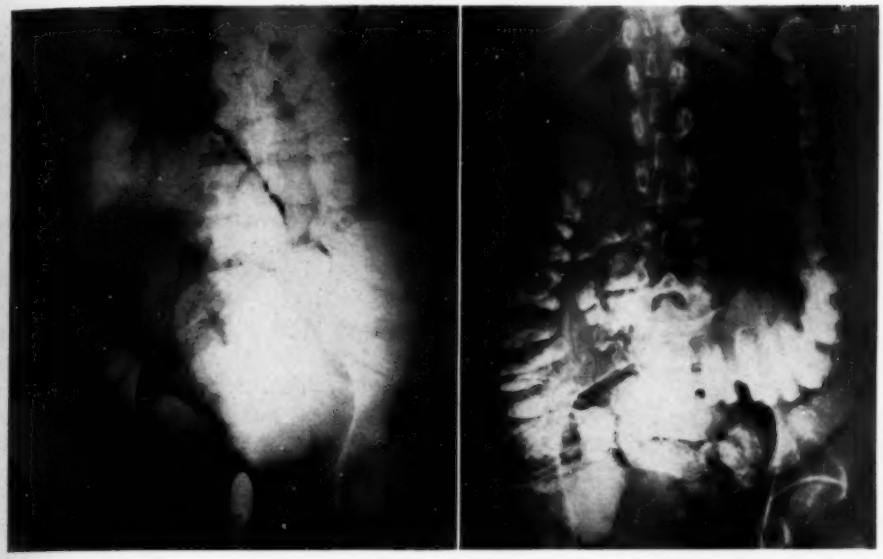

Fig. 12. Markedly atonic colon before and after evacuation of barium enema. The patient was a cathartic addict.

lastly by a co-ordinate relaxation of the anal sphincters. The pressure stimuli can be voluntarily suppressed, the rectum becoming unresponsive after it adjusts its capacity to a fecal bulk. Such seems the beginning of the constipated bowel (Fig. 11).

Both spinal and autonomic nerves supply the colon. The effects of the vegetative system are in the main inhibitory. The vagus gives branches to the proximal half of the colon and the sacral parasympathetics supply the remainder. Stimulation of the latter results in contractions of the bowel wall and relaxation of the anal sphincters. The profound effects of psychic stimuli through a vagus component are fairly well established. The results of sympathectomy for megacolon have been disappointing. It is interesting to note that atrophy and dissolution of the plexuses of Meissner and Auerbach have been observed in megacolon, while hypertrophic changes have been reported in advanced ulcerative colitis (2). It is apparent that many aspects of intestinal neurophysiology and the resultant functional counterparts have not been clearly worked out.

*Pathologic Physiology:* The purely functional manifestations of the gastro-intestinal tract were perhaps first noted in the colon. Here the various psychic and reflex functional changes often give rise to the so-called irritable colon or mucous colitis. The so-called "string sign" was one of the earliest specific signs described in studies of the large bowel. Anyone who has done a number of barium enema studies will appreciate how easily the function of the large bowel is upset without ever proving any organic change. All gradations from marked atonicity and dilatation to a severe diffuse spasm can be seen (Figs. 12 and 13). Certain long-standing functional changes may be the result of voluntary change in bowel habits and/or certain congenital anomalies. The cathartic addict with the sluggish bowel may have his trouble precipitated by various minor congenital anomalies such as abnormal length, attachment, or rotation. These may have been the precipitating factors in the long history of cathartic use. Any evidence of scybala in the rectum will tell us that there is a disturbance in the usual motility of the colon. Normally the rectum must never contain

Fig. 13. Colon film showing spastic areas in the ascending and descending colon. A long "string sign" is shown in the transverse colon.

any fecal material except during the act of defecation.

The pattern of the colon after excessive use of cathartics, as recently described by Heilbrun (9) and Golden (8), seems to deserve some comments, since this picture can simulate organic change but is for the most part reversible. We think it should be considered in the realm of functional disease, particularly since withdrawal of the cathartic will again bring about a relatively normal pattern.

## CONCLUSIONS

From the foregoing discussion, it is evident that the autonomic control of the digestive tract is a complicated mechanism. Experimental studies as well as certain clinical evidence show that the alimentary tube has an inherent mechanism of its own which, if allowed to function by itself, under ordinary conditions, will carry on as an autonomous unit. Certain writers, as Alvarez and Bargen, however, point out that the regulatory effect of the autonomic nervous system is called into action when and if there is a necessity for an added control to modify and correlate this inherent mechanism. Then, and only then, does it become an important factor in the function of the alimentary tube. If we are to accept the chemical mediator theory as the most likely controlling mechanism of tone and contraction and relaxation of smooth musculature, then it is quite evident that this secondary role of the autonomic nervous system may take a prominent part in functional abnormalities of the entire tract or any portion thereof.

We have attempted to show how the roentgen patterns may be altered in the case of various disturbances of body functions both alimentary and extra-alimentary. The radiologist can find much of interest both organically and functionally in the mirror of the gastro-intestinal tract, which so often reflects the general health of the individual.

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SUMARIO

**Hallazgos Roentgenológicos en los Trastornos Funcionales del Tubo Digestivo**

Repásanse los puntos culminantes de la fisiología del tubo digestivo que interesan al roentgenólogo, tratando de correlacionar los desarreglos funcionales de cada segmento con los procesos patológicos orgánicos.

*Esófago:* En el esófago existen tres formas de actividad muscular: las ondas peristálticas primarias, las ondas secundarias debidas a excitación mecánica local y las contracciones terciarias denominadas a veces "rizos." Las ondas secundarias se observan cuando hay pequeñas obstrucciones y asociadas a traumatismo por cuerpos extraños. Los "rizos" pasan por ser debidos a irritación imputable a un proceso patológico subyacente. A falta de inflamación, neoplasia u obstrucción por cuerpo extraño, las disfagias tienen probablemente su origen en el sistema nervioso central o en alguna miopatía primaria.

*Estómago:* El "piloroespasmo aparente" puede ser secundario a colecistopatía o tener por causa estados afectivos. El verdadero piloroespasmo es frecuente en la úlcera duodenal o pilórica o la gastritis ulcerada, pero no está justificado un diagnóstico de úlcera a base exclusiva de irregularidades funcionales. Estas sólo deben ser consideradas como debidas a afección local cuando existe una lesión orgánica bien definida.

*Duodeno:* Los trastornos de la fisiología duodenal rara vez van asociados con una anomalía orgánica bien definida. Sin embargo, una verdadera anorexia nerviosa puede, por la pérdida de peso, con la mayor tracción ejercida sobre la raíz del mesenterio y sus vasos, culminar en obstrucción orgánica real, acentuando el antiperistaltismo observado normalmente en el duodeno y con éstasis real.

*Yeyuno e Ileon:* Los trastornos motores reflejos del estómago, las mesenteropatías y las lesiones retroperitoneales, así como los estados emotivos, las perturbaciones alérgicas y las deficiencias nutritivas, pueden ocasionar trastornos funcionales del intestino delgado.

*Colon:* Las alteraciones funcionales psíquicas y reflejas dan a menudo origen a la llamada irritación colónica o colitis mucosa. El prolongado empleo de catárticos puede provocar un cuadro que simula enfermedad orgánica pero que en su mayor parte es reversible.

Llégase por fin a la conclusión de que el tubo digestivo tiene un mecanismo inherente propio, que si se deja funcionar por su cuenta en las condiciones ordinarias, trabajará como unidad autónoma. No obstante, el papel del sistema nervioso autónomo puede convertirse en un factor importante y desempeñar una misión significativa en las anomalías funcionales de todo el tubo o de parte del mismo.

# External Irradiation with Roentgen Rays and Radium in the Treatment of Human Leukemias, Lymphomas, and Allied Disorders of the Hemopoietic System[1]

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ROENTGEN THERAPY has its established place as a valuable palliative procedure in the treatment of human leukemias, lymphomas, and allied diseases. Its general and local effects in these disorders have been the subject of numerous reports by expert radiologists and hematologists. In the last decade radioactive isotopes and recently the nitrogen mustards have been added to the therapeutic arsenal against these diseases. The purpose of this presentation is to furnish an introduction to the papers[2] on treatment with these new methods rather than to contribute anything new. As a basis for comparison with the results, complications, advantages, and limitations of the therapeutic use of these new compounds, we have reviewed 337 cases of blood dyscrasias treated by external irradiation in Billings Hospital (University of Chicago).

## MATERIAL

The 337 cases represent the number of patients accepted for irradiation therapy from 1929 to 1945. The total number of patients with blood diseases seen in the clinics and in the hospital during that period could not be determined.

The series consists of patients with leukemia, Hodgkin's disease, lymphosarcoma, and polycythemia rubra vera. The small number of patients with polycythemia rubra is included because in this group strides forward with the new agents have been made. In all cases of Hodgkin's disease and lymphosarcoma the diagnosis was verified by biopsy. In 33 per cent of leukemias confirmation was obtained by bone marrow aspiration or biopsy, lymph-node biopsy, or autopsy.

Table I shows the number of cases in each group and some pertinent data. The distribution of the diagnoses is similar to that reported by Craver for the lymphoblastomas seen at Memorial Hospital, New York (3). The most frequently treated condition in both instances was Hodgkin's disease. We were able to keep track of the largest number of patients, relatively, in the leukemia group.

## THERAPY

The routine treatment in all four groups of disease was roentgen therapy given as local irradiation. Table II indicates the limited use of total body or wide-field spray irradiation, radium therapy, and chemical agents supporting or replacing roentgen irradiation. The chemicals were Fowler's solution in myelogenous leukemia, used systematically over long periods, radioactive phosphorus in polycythemia rubra, and nitrogen mustards in selected cases of all groups.

Radical excision of a localized enlarged lymph node, which was the only sign of the disease, was performed in a single case of Hodgkin's disease. Supportive treatment with blood transfusions, iron, vitamins, adequate diet, plenty of rest, exposure to fresh air and sunshine, was used on a large scale and found to be of great importance in all groups.

The roentgen ray quality used by us for the treatment of these conditions is h.v.l. 1.5 mm. Cu (200 kv., 1.0 mm. Cu plus 1.0 mm. Al filter). Only for the treatment

[1] From the Division of Roentgenology, Department of Medicine, The University of Chicago. Presented at the Thirty-second Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 1–6, 1946.

[2] One of these papers, by Spurr, Jacobson, and Taylor, follows (page 387).

TABLE I: SUMMARY OF 337 CASES OF DISEASE OF THE HEMOPOIETIC SYSTEM TREATED BY ROENTGEN THERAPY 1929–1945

| Diagnosis | Number Irradiated Cases | Sex M. | Sex F. | Age Range and Average Age (years) | Duration Before Treatment (months) | Cases Followed |
|---|---|---|---|---|---|---|
| LEUKEMIA | 110 | 62 | 48 | 1–85 | | 81 |
| Chronic myelogenous | 49 | 26 | 23 | 11–69 (42) | 13 | 36 |
| Chronic lymphatic | 51 | 29 | 22 | 2–85 (53) | 20 | 35 |
| Acute (4 myelogenous, 6 lymphatic) | 10 | 7 | 3 | 1–61 (22) | 1.5 | 10 |
| HODGKIN'S DISEASE | 143 | 91 | 52 | 4–51 (35) | 15 | 91 |
| LYMPHOSARCOMA | 77 | 44 | 33 | 2–74 (48) | 10 | 43 |
| POLYCYTHEMIA RUBRA | 7 | 6 | 1 | 24–71 (49) | 6 yr. | 6 |

TABLE II: IRRADIATION METHODS AND SUPPLEMENTARY THERAPY IN 337 CASES OF DISEASE OF THE HEMOPOIETIC SYSTEM, 1929–1945

| Disease | No. of Cases | Roentgen Rays Local | Roentgen Rays Spray | Radium | Radio Phosphorus | Chemotherapy Fowler's Solution | Chemotherapy Nitrogen Mustards |
|---|---|---|---|---|---|---|---|
| LEUKEMIA | 110 | 105 | 15 | 2 | 1 | 22 | 2 |
| Chronic myelogenous | 49 | 48 | 8 | 2 | .. | 20 | 1 |
| Chronic lymphatic | 51 | 50 | 4 | .. | .. | 2 | 1 |
| Acute | 10 | 7 | 3 | .. | 1 | .. | .. |
| HODGKIN'S DISEASE | 143 | 142 | 9 | 1 | .. | .. | 5 |
| LYMPHOSARCOMA | 77 | 76 | 10 | 1 | .. | .. | 6 |
| POLYCYTHEMIA RUBRA | 7 | 6 | 1 | .. | 2 | .. | 1 |

of skin lesions and small superficial nodes do we prefer h.v.l. 0.24 mm. Cu (135 kv., 3.0 mm. Al equivalent intrinsic filtration only). The use of smaller portals and less crossfiring with hard rays is a disadvantage in the treatment of these diseases. The results with radium therapy reported by Craver and others demonstrate that equal effects can be obtained within a wide range of radiation qualities, provided that each part of the diseased tissue receives a sufficient dose and that excessive local and volume doses are avoided.

In the great number of modifications which the roentgen technic has to undergo in its adaptation to the special needs of the individual case, we have adhered, in the last eight years, to the following main principles: In all cases with generalized disease the minimum doses necessary to produce a remission were given. In localized single manifestations of Hodgkin's disease and lymphosarcoma we felt justified in giving high total doses, of the order of 2,000 to 4,000 r in the diseased tissue in a curative attempt. The total treatment time was kept as short as compatible with the patient's condition. As a rule, daily treatments were given, but treatment was limited to one or two areas per day.

Treatment courses were repeated only in the presence of symptoms and signs indicating activity of the disease, not prophylactically. Nor did we give routine prophylactic irradiation to adjacent internal lymph nodes in the treatment of superficial adenopathy. Though we are fully aware of the utmost importance of treating all foci of disease in the earliest phase of development and see a potential advantage of internal irradiation with radioactive isotopes and of chemotherapy in an effect on subclinical foci, we have found it of advantage to keep the average patient under very close surveillance and to direct external irradiation by clinical observation and laboratory findings.

Total body or wide-field spray irradiation was given chiefly to patients in advanced stages of disease, with decreased response to local irradiation. Though, as a rule, remissions were thus obtained,

no instance of essential influence on the course of the disease was observed. In the few cases of chronic leukemia in which this technic was used initially, it became, without exception, after the first remissions, less effective in the control of markedly enlarged lymph nodes and splenomegaly than local irradiation, which was added or substituted.

The radiation quality routinely used in total body or wide-field spray irradiation was h.v.l. 1.5 mm. Cu. In the initial treatment of leukemia a total dose of 50 r $D_0$, in five fractions of 10 r, was most frequently given. The maximum dose applied in advanced stages of Hodgkin's disease and lymphosarcoma was 200 r $D_0$ to the anterior surface of the total body, and an equal amount to the posterior surface.

It appears noteworthy that in two patients with myelogenous leukemia marked clinical and hematological improvement and regression of the splenomegaly were observed after total body irradiation with h.v.l. 0.25 mm. Cu and single and total doses not higher than were routinely given with h.v.l. 1.5 mm. Cu. Studies of the relative effectiveness of different volume doses as given with different radiation qualities are being continued.

Radium therapy of blood diseases has chiefly been practised at institutions in possession of a radium bomb with several grams of radium, in the form of fractionated local irradiation, without essential advantage over roentgen therapy. Though radium is especially suited for continuous irradiation, continuous total body exposure to gamma rays, similar to the exposure to roentgen rays in the Heublein unit of the Memorial Hospital, has not been practised systematically. A method of external irradiation with radioactive isotopes may develop along this line.

Two of the radium treatments listed for our patients were radium bomb treatments given prior to the admission to our clinic. Our two applications illustrate the usefulness of radium as an occasional supplement of roentgen therapy. In a very obese woman with a reticulum-cell sarcoma confined to the pelvic lymph nodes, intravaginal radium application followed external roentgen irradiation. In a second case, a patient in the final stage of Hodgkin's disease, with a huge painful spleen underlying skin with marked radiation damage, an analgesic effect was obtained with a radium mold.

The patients who received nitrogen mustard in addition to irradiation form two groups. The first is composed of patients in advanced stages of Hodgkin's disease and lymphosarcoma who had received extensive irradiation with decreasing response and were carried on with nitrogen mustards. The second group consists of patients with the same diseases, with or without previous roentgen therapy, who were referred for local irradiation after nitrogen mustards had failed to decrease the size of large tumors.

In polycythemia rubra, three different methods of roentgen therapy were tried: 6 patients received conventional local irradiation over the long and short bones; in 2 patients the treatments were directed to the pylorus of the stomach, as recommended by Andersen, Geill and Samuelsen (1), with the object of depressing the intrinsic factor of Castle, which has been associated with the etiology of polycythemia; 1 patient received total body irradiation with the high surface dose of 210 r in eight fractions. In 2 cases final resort was had to the use of radiophosphorus.

## COMPLICATIONS

More than 50 per cent of all roentgen treatments were given to ambulatory patients. The conditions requiring hospitalization and complicating irradiation were more frequently manifestations of the disease than results of treatment. They included fever, chills, severe anemia, dyspnea, hemorrhage, serous effusions, pain, and general malaise. Radiation sickness seldom reached so extreme a degree as is frequently attained by the toxemic reactions after chemotherapy.

Slight to medium depression of the white

blood cell count after irradiation was observed in the majority of cases. Severe leukopenia, with a drop of the white count to less than 2,000 per cubic millimeter, was rare. A drop to 1,000 one month after the discontinuation of roentgen therapy was observed in a single case of chronic myelogenous leukemia. At the time of this observation, we were less familiar with the regularity with which recovery from such low levels occurs than after observations following the use of nitrogen mustard compounds.

In two patients with chronic lymphatic leukemia, agranulocytosis developed after irradiation. Both patients lived for more than two years after this incident.

The hemoglobin and red blood cell count were either not affected or were improved under irradiation in the early stages of disease. These observations served as a valuable guide in the direction of therapy as well as in regard to prognosis. In the late stages, severe anemia precludes irradiation.

A depression of the platelet count after irradiation was observed in patients with a tendency to bleeding prior to therapy, as in acute leukemia and in the final stages of the other disorders.

All late changes, as induration of the skin or subcutaneous structures, are much less frequently observed now than ten years ago. Final severe anemia and leukemoid reactions occur in non-irradiated patients as well as in irradiated ones. To my knowledge, there are no statistical data for comparison.

Roentgen therapy is ineffective in acute leukemia. It is the consensus to regard it as contraindicated unless some local distress, as that caused by large mediastinal lymphadenopathy or splenomegaly, may be relieved by it.

Irradiation fastness is the most frequent limitation of the usefulness of roentgen therapy. It is rarely encountered from the onset but develops with the progress of the disease and of the therapy. Local irradiation changes, as avascularity and excessive fibrosis, need not be present for its development, though they favor it. Radioresistance may show remissions, especially after extensive supportive treatment. In two cases of Hodgkin's disease, non-responsive enlarged peripheral nodes disappeared under renewed irradiation after the general condition of the patients had improved following prolonged vacations in Florida. The technic and dosage were the same as previously, and the interval between courses was too long to assume a cumulative effect. Similar observations were made in patients with generalized lymphosarcoma after series of blood transfusions.

### FOLLOW-UP OBSERVATIONS

On account of the protean nature of Hodgkin's disease and the great variation of the individual course in leukemia and lymphosarcoma, the effectiveness of a palliative measure is extremely difficult to evaluate. Valid conclusions require either the statistical evaluation of a large number of cases or close observation of a smaller number of patients over long periods.

The analysis of our material as to the frequency and degree of regression of various types of foci of disease and the duration of the remissions is fraught with special difficulty. Some of the patients have been seen only sporadically at long intervals. In some, roentgen therapy has been continued at other institutions. The spacing of the irradiation courses is, therefore, far from being a measure for the duration of remissions.

It was possible to determine the length of survival for 221 patients followed from the beginning of therapy until death or to date. In the majority of cases, irradiation was started in our clinic as soon as the diagnosis was made. In a few patients diagnosis had been established elsewhere and was confirmed by us. If the patient had received previous treatments, we dated the survival from the beginning of these treatments; otherwise, from the start of therapy under our direction.

The survival is shown in Tables III to VI for the different diseases.

TABLE III: CHRONIC MYELOGENOUS LEUKEMIA. SURVIVAL AFTER BEGINNING OF THERAPY IN 49 CASES

| Years | Living, 1 | Dead, 35 | Lost to Observation, 13 |
|---|---|---|---|
| Under 1 | .. | 6 (17%) | 4 |
| 1–2 | .. | 7 (20%) | 4 |
| 2–3 | .. | 9 (26%) | 3 |
| 3–4 | .. | 4 (11.5%) | 1 |
| 4–5 | 1 | 4 (11.5%) | .. |
| 5–10 | .. | 5 (14%) | 1 |
| Over 10 | .. | ..... | .. |

Living three years or more, 32.7%.
Average survival to death (35 cases), 33 months.

TABLE IV: CHRONIC LYMPHATIC LEUKEMIA. SURVIVAL AFTER BEGINNING OF THERAPY IN 51 CASES

| Years | Living, 5 | Dead, 30 | Lost to Observation, 16 |
|---|---|---|---|
| Under 1 | .. | 8 (27%) | 11 |
| 1–2 | 1 | 9 (30%) | 2 |
| 2–3 | .. | 3 (10%) | 2 |
| 3–4 | .. | 3 (10%) | 1 |
| 4–5 | .. | 3 (10%) | .. |
| 5–10 | 3 | 4 (13%) | .. |
| Over 10 | 1 | ..... | .. |

Living three years or more, 30%.
Average survival to death (30 cases), 30 months.

*Chronic Myelogenous Leukemia* (*Table III*): Six of 49 patients with chronic myelogenous leukemia lived over five years. Their average survival was six years and five months, the longest eight years and one month. The average survival of 35 patients followed until death was thirty-three months. Sixteen patients, approximately one-third of the whole group without deduction of the untraced, lived three years or more.

These figures are in agreement with those in the newer literature. Craver reported 4 five-year survivals among 69 cases. The average for these 4 patients was six years; for the whole group it was twenty-four months. We did not observe any patients who lived as long as some of Widmann's (8), namely, thirteen and nineteen years.

Four of the six patients who survived over five years had been given Fowler's solution systematically over long periods. The patient with the longest survival was from the beginning treated with very high roentgen doses and remained radioresponsive until death.

*Chronic Lymphatic Leukemia* (*Table IV*): Eight of 51 patients with chronic lymphatic leukemia lived over five years. The average survival of 4 of them followed until death was six years and nine months. The longest survival of one of the 4 followed to date is ten years and six months. The average survival of the 30 followed until death was thirty months. Sixteen patients (30 per cent) of the whole group, including the untraced, lived over three years.

In Craver's material, the number of patients with chronic lymphatic leukemia who lived over five years was 7 of 77 (9.1 per cent). In his group, as in ours, the average survival of the five-year survivors was slightly higher and the average survival of the whole group slightly lower than in chronic myelogenous leukemia. This observation reflects the greater variation of the individual course in the lymphatic form.

In old people chronic lymphatic leukemia frequently takes a relatively benign course. Seven of our 8 long-term survivors were over fifty years of age at the onset of the disease. The only one in the thirties has a leukopenic form of leukemia. This form also tends to progress more slowly. The average survival of 5 patients with leukopenic lymphatic leukemia followed until death was thirty-eight months as compared to thirty months for all 30 patients followed until death. Six of our 8 long-term survivors had an initial white blood cell count of less than 50,000.

All patients with chronic lymphatic leukemia received much less irradiation than those with chronic myelogenous leukemia. The response to small doses locally or over the total body was often striking, and similar to that in certain cases of lymphosarcoma. Remissions of two to four years' duration and even longer were observed after small doses of roentgen rays.

*Acute Leukemia:* All patients with acute leukemia died within two months after treatment and within three months after the onset of symptoms.

TABLE V: HODGKIN'S DISEASE. SURVIVAL AFTER BEGINNING THERAPY IN 143 CASES

| Years | Living, 22 | Dead, 69 | Lost to Observation, 52 |
|---|---|---|---|
| Under 1 | 1 | 20 (29%) | 31 |
| 1-2 | 4 | 16 (23%) | 4 |
| 2-3 | 1 | 11 (16%) | 5 |
| 3-4 | 3 | 9 (13%) | 4 |
| 4-5 | 3 | 4 (6%) | 1 |
| 5-10 | 5 | 7 (10%) | 7 |
| Over 10 | 5 | 2 (3%) | .. |

Living three years or more, 35%.
Average survival to death (69 cases), 32 months.

TABLE VI: LYMPHOSARCOMA. SURVIVAL AFTER BEGINNING OF THERAPY IN 77 CASES

| Years | Living, 8 | Dead, 35 | Lost to Observation, 34 |
|---|---|---|---|
| Under 1 | .. | 24 (69%) | 23 |
| 1–2 | 1 | 5 (14%) | 5 |
| 2–3 | 4 | 4 (11%) | 3 |
| 3–4 | .. | 1 (3%) | 1 |
| 4–5 | .. | ..... | 1 |
| 5–10 | 3 | ..... | 2 |
| Over 10 | .. | 1 (3%) | .. |

Living three years or more, 12%.
Average survival to death (35 cases), 11 months.

*Hodgkin's Disease* (*Table V*): Seven of 143 patients with Hodgkin's disease are known to have lived over ten years, and 26 over five years. Ten of these patients are still living; 9 are known to be dead, with an average survival of nine years and six months; 7 are untraced after observation periods of five years to eight years and four months. The average survival for the total number of patients followed until death is thirty-two months.

Five patients are living after more than ten years, namely, fifteen years, fourteen years and six months, twelve years, eleven years, and ten years and three months. The longest survival until death was fourteen years and eight months. Thirty-five per cent of the total group lived three years or more.

Our pathologists had not, from the beginning, divided the cases of Hodgkin's disease into the three groups of paragranuloma, granuloma, and sarcoma. In re-examining the slides of the 26 patients who were observed longer than five years, we assigned less than 50 per cent to the paragranuloma group. In one of the 26 patients our pathologist and Broders concurred in a diagnosis of Hodgkin's sarcoma.

In 3 of the long-term survivors, the first manifestation of the disease was a localized lymphadenopathy, in 2 patients of peripheral glands and in the third in the mediastinum. In the 2 patients with a peripheral focus the disease remained controlled after a single course with high dosage to this focus. In one case the dose was 3,000 r in ten days at 3 cm. depth in the axilla, followed by a moist epidermite; in the other, 2,600 r $D_0$ in 110 days to a cervical lymph node tumor. The primary focus in the mediastinum received a depth dose of 2,100 r in twenty-one days. No local recurrence became evident, but generalized lymphadenopathy occurred in the second year after the initial therapy.

Six patients of the 26 with a long life span showed mediastinal involvement. In all of them complete or very marked regression was obtained. The minimum depth dose delivered in these cases was 2,000 r in the mediastinum in fifteen to sixty days.

Jackson and Parker (7) have called attention to two points which may or may not indicate a greater efficacy of the more recent roentgen therapy methods in Hodgkin's disease. The first is the steady rise of the five-year survival figures recorded in the literature, from 10 per cent in the report by Desjardins and Ford (4) in 1923 to 18 per cent reported in 1932 from Holfelder's institute and 34 per cent in Gilbert's (5) series in 1939. The second is the different picture presented by the survival figures of the patients followed until death and those of the living patients followed to date. In their own series, the average course of the disease was much longer for those still living. In our material the same difference becomes apparent. But the analyzed series are too small to be beyond statistical error.

*Lymphosarcoma* (*Table VI*): Of 77 patients with lymphosarcoma, one died 13 years after the beginning of therapy. Three patients are living longer than five years, 2 without evidence of disease.

| | No. of Cases | —Until Death— No. of Cases | Survival Aver. mo. | 5 yr. % | To Date Survival 5 yr., % |
|---|---|---|---|---|---|
| 1 Chronic Myeloid Leukemia | 36 | 35 | 33 | 14 | 14 |
| 2 Chronic Lymphatic Leukemia | 35 | 30 | 30 | 13 | 23 |
| 3 Hodgkin's Disease | 91 | 69 | 32 | 13 | 21 |
| 4 Lymphosarcoma | 43 | 35 | 11 | 3 | 9 |

Fig. 1. Survival of 205 cases of diseases of the hemopoietic system from beginning of roentgen therapy until death or to date.

Two patients were lost to observation after five years. Sixty-nine per cent of the patients observed until death died within the first year. Only 12 per cent lived over three years.

The two asymptomatic patients with a life span of more than five years presented localized adenopathies, one in the pelvis and the other in the mesentery. Both received, after exploration, high irradiation doses, of the order of 3,000 to 4,000 r in the lesions. In the other patients with a long life span, including the patient who lived thirteen years, multiple foci of disease were present from the beginning. Primary foci in the mucous membrane of the upper airways were found in only 3 patients of this series.

Of 14 patients in whom an exploratory laparotomy was performed in the presence of a localized tumor causing partial intestinal obstruction, 10 were followed until death. With the exception of the 2 patients at present asymptomatic, who have been observed over five years, all patients died within four months.

A case of lymphosarcomatosis of the bone marrow is of interest because of the markedly better response to nitrogen mustards than to total body irradiation.

Jackson (6) reports a loss of 83 per cent of patients with lymphosarcoma within three years. An even more rapid course, with 87 per cent deaths within two years, was observed by Cutler (2). In spite of great radiosensitivity, few if any cases of lymphosarcoma are radiocurable.

For 164 cases followed until death the curves of Figure 1 show the difference in the life span after onset of therapy for leukemia, Hodgkin's disease, and lymphosarcoma. They do not give correct information on the median duration of each disease, as the material has been collected too recently.

*Polycythemia Rubra Vera:* In our experience the results of roentgen therapy have not been very gratifying in polycythemia rubra. With any of the three different methods used, symptomatic relief was obtained for two to five months. The hematologic effect noticed after treatments directed to the region of the gastric pylorus consisted only in a slight depression of the elevated white blood cell count. After irradiation of the long and short bones, a more marked depression of the white cell count was observed. The depression of the red blood cell count and of the hemoglobin was slight or negative. The splenomegaly remained unaffected.

In only one patient, who received the high surface dose of 600 r over each of ten bones, was a remission of eleven months observed. A second course with conventional dosage was much less effective. This patient died five years after the first roentgen therapy and at least twenty years after the onset of the disease, with a final aplastic anemia and leukemia.

In one patient a good symptomatic response and a spectacular hematologic depression, as seen after internal irradiation with $P^{32}$, was observed after total body exposure to 210 r $D_0$ in eight fractions. The remission, however, lasted only five months.

It appears that for the effective treatment of polycythemia rubra relatively high roentgen doses are required, which cannot be repeated frequently without risk.

## CONCLUSIONS

In conclusion it can be said that roentgen therapy of leukemia, Hodgkin's disease, and lymphosarcoma, judiciously given with the present methods, is an effective palliative measure with a great safety margin and few complications. It finds its broadest indication as local irradiation of the various foci of disease.

The efficacy of total body irradiation as to a systemic effect and the effect on generalized and subclinical foci is less clean cut. It is in these respects that experience with radioactive isotopes and chemical compounds is of special interest and that their therapeutic use might be advantageous.

It is our impression that supportive medication with arsenicals is of real value in myelogenous leukemia. Our experience with nitrogen mustard compounds as a supportive measure does not yet allow valid conclusions.

The dosage required for effective roentgen therapy of polycythemia vera does not allow frequent treatment courses.

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## SUMARIO

### La Irradiación Externa con Rayos X y Radio en el Tratamiento de las Leucemias, Linfomas y Afecciones Afines del Aparato Hematopoyético del Hombre

En el Hospital Billings (Universidad de Chicago) de 1929 a 1945 aceptaron para irradiación un total de 337 enfermos con leucemia, enfermedad de Hodgkin, linfosarcoma y policitemia rubra. En los cuatro grupos el tratamiento habitual consistió en irradiación local con rayos X, complementada en algunos casos con irradiación total del cuerpo o en grandes campos, curieterapia y uso de productos químicos (solución de Fowler en la leucemia mielógena; fósforo radioactivo en la policitemia rubra; mostazas del nitrógeno en todos los grupos). Los habituales factores irradiatorios fueron: 220 kv., filtración por 1.0 mm. de Cu más 1.0 mm. de Al, c. h.-r. 1.15 mm. de Cu. En los enfermos con enfermedad generalizada, se administraron las dosis mínimas necesarias para producir una remisión. En las manifestaciones locales de la enfermedad de Hodgkin y el linfosarcoma, pareció justificado administrar dosis totales altas—2,000 a 4,000 r en el tejido patológico—en un esfuerzo curativo. La duración total del tratamiento fué lo más breve que permitía el estado del enfermo. Por regla general, administráronse tratamientos diarios, limitados a una o dos zonas. Sólo se repitieron las series terapéuticas cuando había signos indicativos de actividad de la dolencia.

Obtuviéronse las siguientes sobrevivencias de cinco años: en la leucemia mielógena crónica (49 casos), 6; en la leucemia linfática crónica (51 casos), 8; enfermedad de Hodgkin (143 casos), 26 (incluso 7 sobrevivencias de 10 años); linfosarcoma (77 casos), 6. Todos los enfermos de leucemia aguda murieron en término de dos meses del tratamiento. El resultado en la policitemia roja también fué desalen-

tador, siendo las dosis requeridas demasiado altas para repetirlas.

De lo anterior se deduce que, en la leucemia, la enfermedad de Hodgkin y el linfosarcoma, la roentgenoterapia, juiciosamente administrada con las técnicas actuales, constituye una eficaz medida paliativa con un gran margen de seguridad y pocas complicaciones. La eficacia de la irradiación total del cuerpo no parece tan clara. En la leucemia mielógena, la medicación tónica con arsenicales parece ser de valor. Las observaciones con las mostazas del nitrógeno como medida tónica fueron demasiado limitadas para poder sacar conclusiones válidas.

# Chemotherapy in Human Lymphomas, Leukemias, and Allied Disorders of the Hemopoietic System[1]

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THE ATTEMPT TO control leukemia by toxic chemicals dates to 1865, when Lissauer obtained marked symptomatic relief following administration of Fowler's solution (potassium arsenite). Cutler and Bradford, in 1878, were the first to quantitate the changes in leukemia by blood studies. After the reports of Pusey in 1902 and Senn in 1903 on the value of roentgen therapy in the disease, the effect of arsenic was largely forgotten. Naegeli, in 1930, recommended arsenical compounds in the control of leukemia, and the studies of Forkner and Scott (1931, 1932) reestablished Fowler's solution as an efficacious adjunct in the treatment of chronic myeloid leukemia. They showed a considerable reduction in the leukocytes with a decrease or disappearance of the immature forms; the anemia was arrested, and frequently there was a marked reticulocytosis. Platelet levels were seldom affected even in the leukopenic phase of treatment. Improvement in the splenomegaly, hepatomegaly, and lymphadenopathy were usually seen. Stephens and Lawrence (1936) fully confirmed these observations. Fowler's solution was found to be most effective in early cases of myeloid leukemia, but Forkner and Scott (1931) demonstrated its value in some cases which had become resistant to roentgen therapy. Today we recognize the limited value of arsenic in controlling early myeloid leukemia and as an adjunct to roentgen therapy.

Benzol represents another notable chemotherapeutic attack upon the leukemias and lymphomas. Korányi (1912), supported by Selling's study (1910–16) of three cases of chronic benzene poisoning, was the first to treat leukemia with benzol. Like arsenic, this compound was most effective against myeloid leukemia. Fear of its irregular and cumulative reaction in the marrow, precipitating an aplastic anemia, has caused Americans to discontinue its use, although it is still favored in a few European clinics. Kalapos (1935) and Forkner (1938) have carefully reviewed the literature and concluded that the injudicious use of benzol together with reports of animal experiments with excessive doses were chiefly responsible for bringing it into disrepute.

In England, Haddow and Sexton (1946) have made a comprehensive study of the effect of several carbamate esters (urethanes) on the growth of animal tumors. These substances, selected because they had been shown to inhibit growth in plants, dramatically retarded the growth of Walker rat carcinoma 256. Clinical trials using urethane and isopropyl phenylcarbonate were then undertaken. Slight amelioration of carcinomas and lymphomas were noted but the results were mainly negative. The observation by Dr. Edith Paterson (1946) that urethane produced a fall in leukocyte count suggested its use in leukemia, and a group of 32 cases was treated. Among 19 cases of myeloid leukemia, 10 were improved for six months or longer and 5 for two months to six months, while 4 cases showed no response. Five of 13 patients with lymphatic leukemia showed a response for six months or more, but 2 of these also received x-ray therapy. In the remaining 8 the response was poor. In those bene-

[1] From the Department of Medicine, The University of Chicago. This work was done under a grant from the American Cancer Society on the recommendation of the Committee on Growth, of the National Research Council. Presented at the Thirty-second Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 1–6, 1946.

TABLE I: SERIAL COUNTS, BY WEEKS, ON STERNAL MARROW FOLLOWING INTRAVENOUS ADMINISTRATION OF METHYL BIS(β-CHLOROETHYL)AMINE HYDROCHLORIDE*

| Cell Types | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| Blasts and promyelocytes | 2.3 | 1.6 | 4.6 | 2.0 | 2.8 | 1.3 | |
| Myelocytes | 15.0 | 9.0 | 10.5 | 17.6 | 10.1 | 7.1 | 12.3 |
| Metamyelocytes | 34.7 | 26.3 | 16.3 | 20.3 | 37.6 | 13.7 | 16.3 |
| Polymorphonuclears | 42.0 | 55.2 | 58.0 | 48.0 | 41.7 | 67.1 | 43.4 |
| Lymphocytes | 3.7 | 6.1 | 6.0 | 10.2 | 14.6 | 17.0 | 17.0 |
| Pro and baso erythroblasts | 6.0 | 1.5 | 2.0 | 8.5 | 7.1 | 3.8 | 3.0 |
| Poly- and orthochromic erythroblasts | 26.0 | 5.0 | 4.3 | 18.3 | 31.3 | 40.3 | 46.0 |
| Nucleated cells × $10^3$ | 100.0 | 87.0 | 29.0 | 17.2 | 65.4 | 53.6 | 45.8 |

* Composite table shows the total nucleated cells and differential counts on sternal marrow aspiration following intravenous injection of methyl bis(β-chloroethyl)amine hydrochloride, 4 doses, average total dose 22 mg.

fited, there was a resolution of the splenomegaly and lymphadenopathy; the hemoglobin increased, and the leukocyte and differential counts reverted to near normal levels. The results suggest that, while this type of therapy may be of value in chronic myeloid leukemia, it is of little or no benefit in acute and lymphatic leukemia.

Our interest in the chemotherapeutic effects of the nitrogen mustard compounds upon neoplasms developed from their characteristic cytotoxic properties. The degree of toxicity of this group of substances parallels the proliferative activity of the cells and is especially striking in the hemopoietic system. Hence, a trial in controlling various blood dyscrasias seemed promising.

Two nitrogen mustard compounds have thus far been studied. Late in 1942, Gilman *et al.* injected tris(β-chloroethyl) amine hydrochloride intravenously in a group of terminal cases of a number of neoplastic diseases. Independently, early in 1943, we began studies on the lymphomas, using methyl bis(β-chloroethyl) amine hydrochloride, and noted a remission of Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia (Gilman and Philips, 1946; Jacobson, Spurr, *et al.*, 1946; Goodman, Wintrobe, *et al.*, 1946; Karnofsky, Craver, *et al.*, 1947; Spurr, Jacobson, *et al.*, 1947). Daily doses of 0.1 mg. per kilogram of body weight have been given in courses of four injections on consecutive days. The toxic reactions consist of nausea and vomiting, which may appear two to three hours following the injection and persist for a similar period. The reaction of the hemopoietic system becomes manifest over a period of three weeks. In the peripheral blood, a lymphopenia develops within one to five days; a leukopenia may be present in the third week but is usually of only one week duration. A variable degree of thrombocytopenia may develop and, with it, an increase in the bleeding time, but purpuric manifestations have been rare. The changes in the peripheral blood are a reflection of injury to the marrow. Serial sternal aspirations and rib biopsies indicate that extreme marrow destruction may occur. Table I is a composite tabulation based upon semiweekly marrow aspirations following a course of 25 mg. of this nitrogen mustard compound. The total nucleated cell count falls from a normal level of 100,000 per cubic millimeter to 17,000 in the third week following treatment. At this stage, there is already evidence of regeneration in the myeloid and erythroid series. This progresses in an orderly manner, and in the sixth week, there is an active regenerative marrow. In the sixth to eighth week following

TABLE II: HODGKIN'S DISEASE. AVERAGE PERIOD OF REMISSION AND INCIDENCE OF LEUKOPENIA FOLLOWING VARIOUS COURSES OF METHYL BIS-(β-CHLORO-ETHYL)AMINE HYDROCHLORIDE

| No. Injections (days) | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| No. cases | 2 | 6 | 6 | 42 | 5 | 18 |
| Average dose (mg.) | 5.2 | 11.9 | 18.9 | 25 | 30.1 | 36.7 |
| Percentage of leukopenia less than 2,000 | 0 | 16 | 66 | 54 | 40 | 54 |
| Average remission in months | 0.75 | 1.6 | 2.0 | 2.2 | 1.6 | 3.3 |

TABLE III: CUMULATIVE EFFECT OF REPEATED DOSES OF METHYL BIS(β-CHLOROETHYL)AMINE HYDROCHLORIDE*

| Cumulated dose (mg.) | 0–50 | 50–100 | 100–150 | 150–200 | 200–300 |
|---|---|---|---|---|---|
| Number of courses of drug | 15 | 15 | 12 | 9 | 7 |
| Average cumulated dose | 29.1 | 76.5 | 120.8 | 175.9 | 251.7 |
| Average dose of last course | 24.2 | 25.3 | 23.4 | 26.0 | 26.7 |
| Average leukocyte count, pre-treatment | 8,880 | 7,710 | 6,355 | 6,930 | 6,320 |
| Average minimum leukocyte count, post-treatment | 4,410 | 2,930 | 2,860 | 2,660 | 2,230 |
| Average per cent fall of leukocytes | 61.3 | 66.2 | 66.0 | 62.2 | 64.8 |
| Average per cent fall of neutrophils | 61.5 | 58.3 | 63.5 | 68.8 | 72.1 |
| Average per cent fall of lymphocytes | 55.4 | 48.8 | 56.2 | 56.5 | 54.8 |
| Per cent incidence of leukopenia <3000 | 40 | 46.6 | 58.2 | 66.8 | 86.9 |

* This table shows the reaction of the peripheral blood to four injections, total dose 24 to 28 mg. Courses are grouped according to the sum total cumulated dose in order to evaluate the effect of repeated doses.

therapy, the marrow cellularity returns to normal limits.

In utilizing therapeutically the cytotoxic properties of a compound, a dose must be selected which does not seriously injure vital tissue. The affinity of the nitrogen mustard compounds for the hemopoietic cells suggests that the margin of safety may best be evaluated by following the leukopenic reaction after a course of treatment. Table II illustrates the incidence of leukopenia and the average remission (in months) following courses of one to six consecutive daily injections. In 54 per cent of the cases receiving a course of four injections, average total dose 25 mg., a leukopenia of 2,000 cells per cubic millimeter, or less, developed. Not until this dose was reached did a leukopenia of 1,000 appear, and with higher doses the duration and severity of leukopenia increased. The average remission following such a course is 2.2 months, or one month longer than is required for complete regeneration of the bone marrow. Thus, a course of four consecutive daily doses totaling 25 to 30 mg. was selected tentatively as most efficacious.

Experience with chemotherapeutic agents has taught us that consideration must be given to the possible cumulative effects upon the bone marrow. Thus far, we have cumulated doses up to 300 mg. To evaluate the reaction of the hemopoietic system, we have grouped the cases in 50-mg. steps and compared the average reaction of leukocytes at pre-treatment and post-treatment levels, as well as the incidence of leukopenia (Table III). We have noticed a slight, and as yet insignificant, lowering of the leukocytes and an increase in the incidence of leukopenia in the patients receiving a cumulative dose of 300 mg. This study must be extended to levels of 600 mg., since this cumulated dose will be reached in treating a case over the average duration of Hodgkin's disease. We have not found any cumulative suppression of the erythrocytes which could be assigned to the drug. At present, there is only equivocal evidence that an inherent hypoplasia of the marrow may develop.

The clinical studies with nitrogen mustards are still too brief to discuss definitive results. Over a four-year period, we have used methyl bis(β-chloroethyl) amine hydrochloride in a variety of malignant conditions of the hemopoietic system. The remissions produced in Hodgkin's disease (one to ten months), lymphosarcoma (one to ten months), chronic lymphatic leukemia (two to twenty-four months), and myelogenous leukemia (zero to three months) are no longer, and occasionally shorter, than those produced by roentgen therapy. There is no indication that remissions were produced in reticulum-cell sarcoma, acute leukemia, multiple myeloma, and sympathicoblastomas. Variable but probably significant remissions have been observed in polycythemia rubra.

Three cases are summarized to illustrate the response following treatment.

TABLE IV: CASE I. BIOPSY DIAGNOSIS HODGKIN'S DISEASE. MALE AGED 51. ONSET IN 1940

X-Ray Therapy
(200 kv., 20 ma., Thoraeus filter, 19 r/min. in air)

| | Size of Ports (cm.) | No. Treatments | Dose per Treatment | Course and Total Result |
|---|---|---|---|---|
| Series I: 4/7–4/22/41 | | | | |
| Left neck | 10 × 10 | 10 | 200 r | 4,000 r in 14 days. Remission for approximately 9 months |
| Posterior mediastinum | 10 × 10 | 10 | 200 r | |
| Series II: 9/12–9/24/42 | | | | Remission for approximately 6 months |
| Anterior mediastinum | 10 × 10 | 5 | 250 r (3), 250 r (2) | 1,150 r |
| Posterior mediastinum | 12 × 15 | 5 | 200 r (1), 250 r (4) | 1,200 r in 12 days |
| Series III: 1/3–1/15/44 | | | | |
| Left axilla | 10 × 10 | 11 | 200 r | 2,200 r. Partial remission one month. Local recurrence and fever |

Methyl bis (β-Chloroethyl)amine Hydrochloride

| | Total Dose (mg.) | Hemoglobin, max.-min. (gm.) | Erythrocytes, max.-min. (×10⁶) | Leukocytes, max.-min. | Leukopenia <3,000 (days duration) | Remission (months) | Remarks |
|---|---|---|---|---|---|---|---|
| I. 5/17–5/20/44 | 26.8 | 10.8 11.6 | 3.17 3.34 | 10,100 1,700 | 4 | 3 | Resolution of lymphadenopathy, (peripheral and mediastinal) |
| II. 8/24–8/27/44 | 29.4 | 12.9 11.3 | 4.31 3.50 | 5,400 1,200 | 10 | 3 | Anemia improved; hilar enlargement only sign of activity |
| III. 12/20–12/24/44 | 30.8 | 14.0 14.4 | 4.2 4.3 | 6,000 2,000 | 7 | 3 | As above |
| IV. 4/13–4/17/45 | 25.6 | 12.8 11.5 | 3.8 | 9,100 5,400 | 2 | 2.5 | Axillary, cervical, and hilar nodes resolved |
| V. 7/19–7/21/45 | 20.4 | 10.5 12.5 | 3.64 3.8 | 3,525 1,100 | 21 | 3 | Resolution of all lymphadenopathy following HN 2 |
| VI. 11/22–11/26/45 | 27.8 | 11.3 | 3.1 | 12,000 | 0 | 2.5+ | Response as above |
| VII. 3/3–3/6/46 | 27.8 | 12.0 10.6 | 3.6 3.4 | 11,250 3,100 | 15 | 2.0 | Response as above; hilar mass enlarging at two months |
| VIII. 5/7–5/11/46 | 28.0 | 11.7 10.8 | 3.6 3.2 | 7,100 1,200 | 7 | 3.0(?) | Symptoms improved; hilar mass partially resolved; quiescent two months |
| IX. 8/5–8/9/46 | 26.4 | 11.5 10.5 | 3.7 3.4 | 7,500 2,000 | 5 | Partial | Symptoms improved; hilar mass enlarging |
| X. 12/17–12/20/46 | 24.0 | 10.5 13.5 | 4.2 5.2 | 7,500 | ... | None | Transfusion 12/21. Respiratory obstruction improved. Death 1/7/47 |

X-Ray Therapy
(180 kv., 20 ma., 1.0 mm. Al filter; 50 cm. F.S.D., 35 r/min. in air)

| | Size of Ports (cm.) | No. Treatments | Dose per Treatment | Course and Total Result |
|---|---|---|---|---|
| Series IV: 9/20–10/10/46 | | | | |
| Left anterior chest | 15 × 11<br>15 × 15 | 8 | 200 r (2)<br>300 r (3), 250 r (3) | 2,800 r in 20 days. No change in mediastinal mass |
| Left posterior chest | 15 × 15 | 3 | 250 r | |
| Series V: 11/1–11/16/46 | | | | |
| Anterior abdomen | 12 × 17 | 4 | 200 r (1), 300 r (3) | Some symptomatic improvement |
| Right posterior abdomen | 10 × 15 | 4 | 200 r (1), 300 r (3) | Progressive evidence of mediastinal obstruction. Return of abdominal pain in three weeks. 3,400 r in 16 days |
| Left posterior abdomen | 10 × 15 | 4 | 300 r | |

TABLE V: CASE II. BIOPSY DIAGNOSIS LYMPHOSARCOMA. FEMALE AGED 24 YEARS. INITIAL SYMPTOMS IN 1943. NO PREVIOUS THERAPY

| Methyl bis(β-chlorethyl)amine HCl Daily doses | | Hemoglobin, max.-min. (gm.) | Erythrocytes, max.-min. (× 10⁶) | Leukocytes, max.-min. | Remission (months) | Duration of Leukopenia, <3000 (days) | History: Abdominal cramps, nausea, vomiting, weight loss, for two years. Examination: Generalized lymphadenopathy; abdominal mass 8 cm. in diameter. X-ray: Abdominal mass extrinsic to bowel. |
|---|---|---|---|---|---|---|---|
| Date 4/15/44 | 20.0 mg. | 13.9–11.6 | 4.0–3.6 | 7,900–2,500 | 2 | 7 | Resolution of peripheral lymphadenopathy and abdominal mass |
| 6/23/44 | 10.0 mg. | 12.5–12.2 | 3.6–3.5 | 4,900–3,000 | 2.5 | 0 | Therapy given before nodes or symptoms recurred |
| 9/30/44 | 10.0 mg. | 12.0 | 3.77 | 4,700 | 1.0 | 0 | Only indication of activity was palpable mass. Resolved after therapy |
| 10/30/44 | 5.0 mg. | 13.1 | 4.10–4.00 | 5,900–4,000 | 2.5 | 0 | Same |
| 11/11/44 | 5.0 mg. | 13.1 | | | | | |
| 1/26/45 | 15.0 mg. | 12.6 | 4.20 | 3,450 | 3.0+ | 0 | Same |
| 3/30/45 | 15.0 mg. | 13.4 | 4.10 | 3,960 | 4.0 | 0 | Same |
| 9/1/45 | 15.0 mg. | 12.6 | 4.00 | 6,300 | 3.0 | 0 | Same |
| 12/26/45 | 15.0 mg. | 13.0 | 3.52 | 5,000 | 3.0+ | 0 | Same |
| 4/17/46 | 15.0 mg. | 13.5 | 3.91 | 6,400 | 3.0+ | 0 | Same |
| 8/15/46 | 15.0 mg. | 15.4 | 4.52 | 4,100 | 3.0+ | 0 | Continues in good health; occasional abdominal distress one to two weeks prior to treatment. No lymphadenopathy. No palpable mass. (February, 1948) |

CASE I (*Hodgkin's Disease*): F. G., a 51-year-old clergyman, was first seen in the Hematology Clinic on April 27, 1944. He gave a history of left cervical lymphadenopathy developing in May 1940. A biopsy was diagnostic of Hodgkin's disease. Roentgenographs of the chest showed a prominence of the hilar nodes. In April 1941, roentgen therapy was given to the left cervical and posterior mediastinal area, totaling 4,000 r (in air) in fourteen days. This produced a remission for nine months. In September 1942, because of fever, weakness, anemia, and lymphadenopathy, a second course of roentgen therapy was given to the mediastinum, totaling 2,350 r in twelve days. A remission of six months followed. The third series of roentgen therapy was given in January 1944, because of marked symptoms, to a large group of tender nodes in the left axilla. A remission of only one month followed this course of therapy, and the roentgenologist felt that the patient was becoming resistant to therapy.

In May 1944, the first course of nitrogen mustard was given, following which there were resolution of lymphadenopathy and improvement in general health. This was maintained by repeating courses of nitrogen mustard every three to four months. In May 1946, the mediastinal mass began to enlarge two months following therapy, and two additional courses caused only partial resolution. Roentgen therapy was instituted again in September 1946 and a course of 2,800 r directed to the mediastinum in a twenty-day period produced no change in the mass. In November 1946, a fifth course of x-ray therapy was directed to the posterior abdomen. This produced improvement only in the abdominal symptoms. A tenth course of nitrogen mustard was given in December but, despite symptomatic improvement, the patient died on Jan. 7, 1947. A detailed summary of his course is presented in Table IV.

CASE II (*Lymphosarcoma*): A 22-year-old technician consulted her physician on March 30, 1944, because of recurring intense, cramping, abdominal pain. This had been present intermittently for two years but only in the past two months had the patient noticed malaise, low back pain, and more frequent attacks of left upper quadrant pain. Physical examination revealed cervical, axillary, right epitrochlear, and inguinal nodes 0.5 to 1.5 cm. in diameter. There was a mass 8 cm. in diameter in the left upper quadrant, but the spleen and liver were not palpable. Blood studies showed 13.3 gm. hemoglobin, 4,200,000 erythrocytes, 9,100 leukocytes. Chest films showed no abnormality. Contrast fluoroscopy of the abdomen indicated that the mass was extrinsic to the bowel. A biopsy of a lymph node was diagnostic of lymphosarcoma.

On April 15, 1944, a series of four consecutive daily injections of 5.0 mg. of nitrogen mustard was begun. Within one week, there was marked resolution of the lymphadenopathy and abdominal mass. There were no longer complaints of cramps or back pains. This remission continued for two months, when the abdominal mass was again present, measuring 3 cm. in diameter. The patient has had seven courses of therapy and, as seen in Table V, lymphadenopathy, body weight, and peripheral blood are well controlled. After thirty-six months, she has no

anemia or leukopenia and continues in normal health, working daily.

CASE III (*Polycythemia*): W. K., female, aged 60 years, was admitted to the Hematology Clinic on Feb. 2, 1945, because of known polycythemia since 1942. In 1938, she was told she had hypertension. Over the previous decade, she had frequent headaches, dizziness, and aching over the extremities of the body. From 1942 until December 1944, she had received various doses of acetyl phenylhydrazine, which only partially controlled the erythrocyte volume as determined by the hematocrit. In the three months prior to admission, she had progressive "fullness of the head," dizziness, and lassitude.

The patient was a moderately obese female whose skin had a generalized red flush. The mucous membranes were engorged with blood. The optic fundi showed moderate arteriolar spasm and marked venous distention. The heart was moderately enlarged, with a systolic murmur at the apex transmitted laterally. The blood pressure was 174/98. The spleen extended 8 cm. below the costal margin and the liver 5 cm. Electrocardiographic and x-ray studies were confirmatory of the above observations.

At the time of admission, the hematocrit reading was 69 per cent, hemoglobin 23 gm., erythrocytes 6,930,000, leukocytes 9,700. The differential count showed 72 per cent neutrophils, 16 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophils. In the interval from February 1945 to September 1945, the hematocrit reading was held near normal levels by phlebotomies. The patient returned to the Clinic in September 1946, having been without treatment for three months. At this time, the hematocrit reading was 61 per cent, hemoglobin 16.8 gm. per cent, erythrocytes 6,100,000, and leukocytes 12,000. The patient was hospitalized and, following three phlebotomies which reduced the hematocrit reading to 51 per cent, received a course of four intravenous injections of nitrogen mustard, totaling 25.2 mg. This was tolerated without leukopenia, and in the following two months the hematocrit reading decreased to 42 per cent. Four months following treatment, the cell volume had risen to 54 per cent. A second course of three injections, totaling 19.5 mg. of nitrogen mustard, was given from Feb. 6 to 8, 1947, which produced a decline of the hematocrit figure to 45 per cent. The cell volume continues to remain within a normal range.

This group of cases illustrates the results which may be obtained with nitrogen mustards in early cases of hemopoietic dyscrasias. Case I is typical of the group of cases which had received roentgen therapy with diminishing remission over a period of time, three years in this instance. There was a remarkable improvement in health during the two years on nitrogen mustard; lymphadenopathy, fever, and anemia were controlled. From August 1946 until death, no significant response was obtained either to nitrogen mustard or roentgen therapy. In a group of 40 cases of Hodgkin's disease, 14 have been given nitrogen mustard therapy after extensive irradiation with x-ray produced only partial remissions. Seven patients have responded well and continue under treatment, 2 failed to show any remission, and 5 had remissions of three to ten months, with death following. In many of these cases, it appeared that a remission was achieved because the disease was in an active state throughout the body. The systemic injection of nitrogen mustard was able to attack these foci of tumor simultaneously. This experience has suggested that the usefulness of this type of therapy may be as a systemic adjunct in conjunction with local roentgen therapy.

There is a marked variation in the response of lymphosarcoma to nitrogen mustard. Eight cases have been treated; of these, 2 showed no significant remission. The remaining 6 have had excellent remissions with repeated courses for a period of eight to thirty-six months. It appears that the degree of invasive malignancy of the tumor is a major factor in determining the response.

In polycythemia, the remissions are variable but usually of sufficient duration to be of clinical significance. Thus far, 7 cases have received nitrogen mustard with remissions in each, varying from four to twelve months.

In conclusion, we have mentioned the major attempts to control hemopoietic neoplasms by chemotherapy. Arsenic is of use as an adjunct to roentgen therapy in controlling myelogenous leukemia. Benzol is no longer used because of the danger of permanent bone marrow damage. Preliminary results suggest that urethane may be a useful adjunct in controlling chronic myeloid leukemia. The problem of dosage and the limiting toxic effects of the nitrogen mustard compounds have been surveyed. Methyl bis(β-chloroethyl)

amine hydrochloride may produce remissions in Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia, but the results are not superior to those of roentgen therapy. A remission may be obtained in cases which are no longer responsive to roentgen therapy. On this basis, it is suggested that a program of treatment utilizing nitrogen mustard as a systemic adjunct to local x-ray therapy may be worthy of investigation. Clinical remission has been produced in polycythemia, but preliminary data do not suggest that it is superior to that which may be produced by $P^{32}$.

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## SUMARIO

### La Quimioterapia en los Linfomas, Leucemias y Trastornos Afines del Aparato Hematopoyético del Hombre

Repásanse los principales esfuersos realizados para cohibir las neoplasias hematopoyéticas por medio de la quimioterapia. El arsénico ha resultado de valor como adyuvante de la roentgenoterapia en la leucemia mielógena y los resultados preliminares indican que el uretano puede mostrar utilidad semejante. Ya no se emplea el benzol por el peligro de producir lesiones permanentes en la médula ósea.

El trabajo actual versa principalmente sobre el clorhidrato de metilo-bis(β-cloroetilo)amina, una de las mostazas del nitrógeno, cuyas propiedades citotóxicas y afinidad para el aparato hematopoyético han conducido a probarlo terapéuticamente en varias hemodiscrasias. La reacción a las inyecciones de este compuesto se traduce en la sangre periférica por una linfopenia que aparece en término de uno a cinco días y por una leucopenia de poca duración. Las aspiraciones seriadas del

esternón indican que puede sobrevenir destrucción extrema de la médula ósea, seguida de regeneración a las pocas semanas.

Tratando de establecer un margen de seguridad al emplear clorhidrato de metilo-bis(β-cloroetilo)amina, observóse la reacción leucopénica tras series de una a seis inyecciones diarias, y sobre esa base se escogió tentativamente como más eficaz una serie de cuatro dosis diarias consecutivas que sumaban 25 a 30 mg. También se estudiaron los efectos de dosis acumulativas hasta de 300 mg. En los enfermos que recibieron esa dosis máxima observáronse baja insignificante de la fórmula leucocitaria y mayor incidencia de leucopenia. No se notó supresión acumulativa de los eritrocitos, y sólo datos equívocos de que puede presentarse hipoplasia inherente de la médula ósea.

Clinicamente, se determinó que el compuesto utilizado puede producir remisiones en la enfermedad de Hodgkin, el linfosarcoma y la leucemia linfática crónica, pero el resultado no es superior al obtenido con la roentgenoterapia, aunque se logran remisiones en casos que ya no responden a la última. Partiendo de esa base, puede ser digno de investigación un plan terapéutico que utilice la mostaza de nitrógeno como coadyuvante general de la roentgenoterapia local. En la policitemia se ha producido remisión clínica, pero los datos preliminares no sugieren que sea superior a la con fósforo radioactivo.

# A Simple Pelvimeter to Be Used with the Triangulation Method of Pelvimetry[1]

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THE PURPOSE of this paper is to present a simple pelvimeter for use with the triangulation method of pelvimetry. This pelvimeter has proved useful in two respects: First, it has resulted in considerable time saving in the correction of pelvic measurements. Second, it has led to increased accuracy by elimination of steps involved in the usual methods of correction.

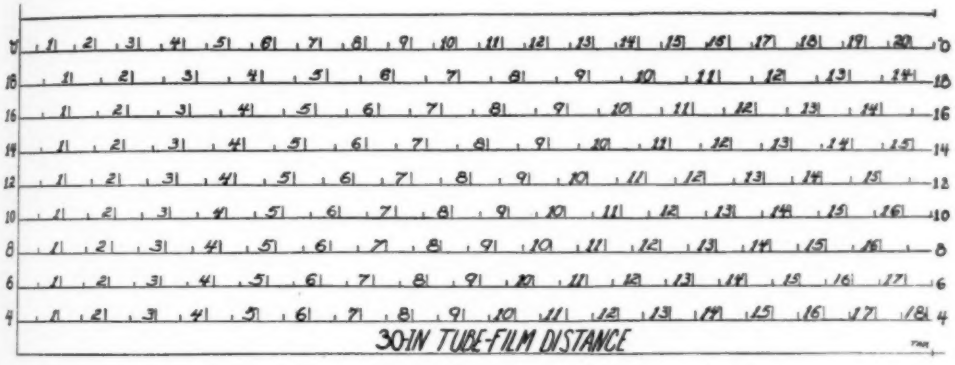


Chart I. Chart for 30-inch tube-film distance. Line 0 is a true centimeter scale; the remaining lines are false centimeter scales. (Reduced to approximately two-thirds actual size.)

## CONSTRUCTION OF THE PELVIMETER

The construction of the pelvimeter is based on the well known and simple principle of similar triangles, in which the true object measurement is to the film measurement as the tube-object distance is to the tube-film distance. This is expressed by the formula:

$$X = F \frac{(H - D)}{H}$$

in which $X$ is the object measurement, $F$ the film measurement, $H$ the tube-film distance, and $D$ the object-film distance. With the use of this formula, a set of values was obtained to construct a chart having nine parallel lines (Chart I). The first line is a true centimeter scale. The remainder are false centimeter scales used in correction of image measurements of objects at various heights above the table top. For example, line 18 is used for correction of film images of objects 18 cm. above the table top. Line 4 is used for correction of film images of objects 4 cm. above the table top. Charts were prepared for both 30-inch and 40-inch tube-film distance. Copies of these charts were made by a local printer. To the back of the charts is pasted a table showing the relationships between diameters, circumferences, and volumes.

A local plastic firm sealed the chart between two thin sheets of plastic, using a laminating press (Fig. 1). To the left side of the plastic-enclosed chart is fixed a pointer, the medial edge of which is continuous with the left-hand vertical line on the chart. A slide was constructed. At

[1] Read before the Radiological Section of the Los Angeles County Medical Association, February 12, 1947. Accepted for publication in March 1947.

Fig. 1. The pelvimeter. 1. Pointer fixed to left of plastic enclosed chart. 2. Pointer on slide. 3. Vertical hair line on slide. 4. Segment of watch spring to maintain pressure of slide on chart. (Reduced to nearly half actual size.)

the upper end is a pointer. Continuous with the medial edge of this pointer is a vertical hair line on the face of the slide. At the lower end of the slide is a segment of watch spring to maintain the pressure of the slide on the chart. On the face of the slide are numbers corresponding to those heading the horizontal lines, to facilitate identification of the particular horizontal line. By moving the slide, any distance can be encompassed between the medial edges of the pointers.

## USE OF THE PELVIMETER

Different writers on pelvimetry select different points for the exact location of the various pelvic diameters. The method of using the pelvimeter is the same regardless of the location of these diameters. In the illustrations to be given, the location is essentially as described by Snow and Lewis (1, 2), the pelvimeter being used to facilitate correction of the measurements.

A lateral and anteroposterior pelvic roentgenogram are all that are required. (In practice we obtain an anteroposterior stereoroentgenogram to study the birth canal stereoscopically.) Correction factors are necessary for the various diameters as seen in both the anteroposterior and lateral film. In the anteroposterior film, since the diameters lie at different heights above the table top, a different correction factor is needed for each. In the lateral film, however, all of the desired diameters lie in the mid-sagittal plane, and only a single correction factor is needed. One half of the external bitrochanteric diameter gives the height of the mid-sagittal plane above the table top and is, then, the correction factor for all diameters measured on the lateral film. The external bitrochanteric diameter is easily measured by the technician at the time that the films are made (the technic rule being useful for this).

Only sufficient examples to illustrate the use of the pelvimeter with this method of pelvimetry will be given.[2]

*The True Conjugate* (*Anteroposterior Diameter of the Inlet*): To obtain the true conjugate, on the *lateral film* the pelvimeter pointers are placed at points A and B (Fig. 2). The value of this diameter is then read

[2] For a complete discussion of this method of pelvimetry, the reader is referred to Snow and Lewis (1) and Snow (2).

where the vertical hair line on the slide (Fig. 1) crosses the horizontal line corresponding to the correction factor for the lateral film, that is, one-half the external bitrochanteric diameter.

*For example:* Suppose that the slide (Fig. 1) is in the position where the pointers are at the ends of the true conjugate. Assume that the external bitrochanteric diameter is 32 cm.; the "correction factor" for all measurements on the lateral film would be one-half of this, or 16. The true conjugate is read on line 16 where the hair line crosses it. In this example the value would be 14.2 cm.

Or assume that the external bitrochanteric diameter is 34 cm.; then the "correction factor" for all measurements in the lateral film would be 17. Since the correction factor numbers at the ends of the horizontal lines are all even numbers, it is necessary to interpolate between these when the correction factor is an odd number. In this example we would obtain the desired true conjugate by interpolating between the lines 16 and 18 (Fig. 1), reading the value as 14.0 cm. This interpolation is always readily accomplished, as the difference between any two consecutive lines does not exceed 1.0 cm.

*Posterior Sagittal Diameter of the Outlet:* To obtain the posterior sagittal diameter of the outlet, it is first necessary to locate the ends of this diameter on the *lateral film*. The posterior point is, of course, the tip of the sacrum at the sacrococcygeal joint, point C (Fig. 2). The anterior point is obtained as follows: A line is extended posteriorly along the inferior margin of each obturator foramen until it intersects the posterior aspect of the ischium. The mid-point between the posterior aspect of the two ischii is marked, point D (Fig. 2). The pelvimeter pointers are placed at the points C and D, and the posterior sagittal diameter is read where the vertical hair line crosses the horizontal line corresponding to the correction factor for the lateral film (that is, one-half the external bitrochanteric diameter).

Any other desired pelvic diameters located in the mid-sagittal plane are obtained in an identical manner.

As mentioned earlier, to obtain the transverse diameters as seen in the anteroposterior film (Fig. 3), it is necessary to obtain a different correction factor for each

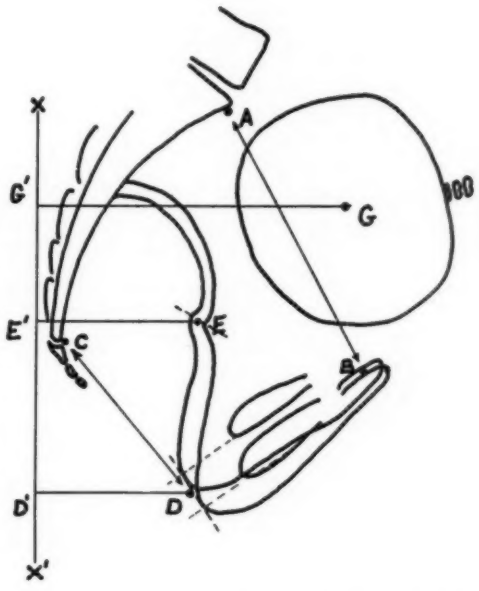


Fig. 2. Lateral view. X-X'. Vertical base line 0.5 cm. posterior to the sacrum and parallel to the film edge. A. Promontory of the sacrum. B. Mid-point of posterior aspect of the symphysis. C. Tip of sacrum. D. Mid-point on bi-ischial diameter. E. Mid-point on intraspinous diameter. G. Mid-point on fetal skull.

diameter, as each lies at a different height above the table top. The correction factors for these diameters are obtained from the *lateral film* (Fig. 2) in the following manner:

Approximately 1.0 cm. posterior to the sacrum a vertical line is drawn parallel to the film edge. This corresponds to the location of the table top when the patient is lying supine for the anteroposterior film. Lines drawn perpendicular to this to the mid-points of the various transverse diameters as seen in the lateral film represent the height of these transverse diameters above the table top. However, since each of these heights lies in the mid-sagittal plane, they must be corrected for distortion. The correction factor is, of course, that for all measurements on the lateral film, namely, one-half the external bitrochanteric diameter.

*Bi-ischial Diameter* (*Transverse Diameter of the Outlet*): Since the point D (Fig. 2) represents the mid-point on the bi-ischial

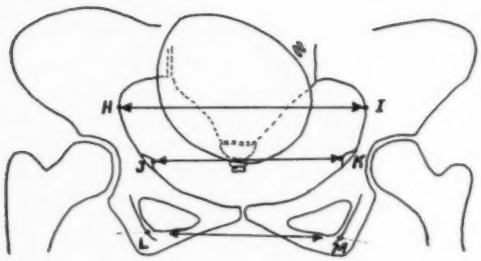


Fig. 3. Anteroposterior film. L-M. Bi-ischial diameter. J-K. Intraspinous diameter. H-I. Maximum transverse diameter of the inlet.

diameter as seen in the lateral view, D-D′ represents the height of this diameter above the table top. The pelvimeter pointers are placed at the points D and D′ (Fig. 2) and the "new correction factor" read on the line corresponding to one-half the external bitrochanteric diameter. This "new correction factor" is read to the *nearest whole number*. On the *anteroposterior film*, the pelvimeter pointers are placed at the ends of the bi-ischial diameter, points L and M (Fig. 3). The bi-ischial diameter is read on the line headed by the number of the "new correction factor" just obtained from the lateral film.

*For example:* Assume that the external bitrochanteric diameter is 36 cm.; then the correction factor for the lateral film would be half of this, 18. Assume that, with the pelvimeter pointers placed at the points D and D′ (Fig. 2), the hair line crosses the line 18 at 5.8 or, to use the nearest whole number, 6. Then the "new correction factor" would be 6. The pelvimeter pointers would then be placed at the points L and M (Fig. 3) and the bi-ischial diameter read on the line 6 where it is crossed by the hair line.

*Intraspinous Diameter (Transverse Diameter of the Mid-Pelvis)*: The intraspinous diameter is obtained in the same manner as the bi-ischial. On the *lateral film*, the midpoint between the posterior aspect of the ischial spines is marked, point E (Fig. 2). The pelvimeter pointers are placed at the points E and E′. The "new correction factor" is read on the line corresponding to one-half the external bitrochanteric diameter. This, also, is read to the *nearest whole number*. On the *anteroposterior film* the pelvimeter pointers are placed at the medial edges of the ischial spines, points J and K (Fig. 3). The intraspinous diameter is read on the line corresponding to the "new correction factor" just obtained from the lateral film. Other transverse diameters are obtained in a like manner.

## AVERAGE FETAL HEAD CIRCUMFERENCE AND VOLUME

With the fetal head engaging or engaged, the perimeter as seen in the *lateral film* is essentially in the mid-sagittal plane; hence, the correction factor is the same as for other measurements in the lateral film, that is, one-half the external bitrochanteric diameter. To obtain a correction factor for the fetal head perimeter as seen in the anteroposterior film, the procedure is identical to that for obtaining the "new correction factor" for the transverse pelvic diameters as described above. In this case the mid-point of the fetal skull as seen in the *lateral film* would be marked, point G (Fig. 2). Then the line G-G′ would represent the height of the perimeter above the table top when the patient is supine for the anteroposterior film.

As described by Snow and Lewis (1, 2), a piece of 1 cm.-wide adhesive 50 cm. long is rolled with the adhesive side out to form a sticky string. This is placed around the perimeter of the fetal skull as seen in the *lateral film* (Fig. 2), folded where the ends of the string meet, removed, and measured on a centimeter rule. It will be recalled that line 0 on the pelvimeter (Fig. 1) is a true centimeter scale, reading up to 20.5 cm. Since in all but the smallest fetuses, the uncorrected perimeter will exceed 20.5 cm., the length obtained by measuring it with the adhesive string is divided by two to obtain the uncorrected half perimeter. The hair line of the slide is placed over the uncorrected half perimeter value and the corrected half perimeter is read on the line corresponding to one-half the external bitrochanteric diameter. This is doubled to

give the total corrected perimeter value as seen in the lateral film.

On the *lateral film* the pelvimeter pointers are placed at the points G and G′ (Fig. 2) and the "new correction factor" is read on the line corresponding to one-half the bitrochanteric diameter, reading to the *nearest whole number*. The uncorrected perimeter as seen on the anteroposterior film (Fig. 3) is measured with the piece of adhesive string as above. The uncorrected value is again divided by two to give the uncorrected half perimeter. The hair line is placed over this value on line 0 of the pelvimeter, and the corrected half perimeter value is read on the horizontal line corresponding to the "new correction factor" just obtained from the lateral film.

*For example:* Suppose the external bitrochanteric diameter is 32 cm.; the correction factor for the lateral film would be 16. The pelvimeter pointers would be placed at points G and G′ (Fig. 2), and the "new correction factor" read on line 16. Assume that this reads 11.8 or, to the nearest whole number, 12; then, 12 is the "new correction factor." Say that the perimeter measured with the piece of rolled adhesive on the *anteroposterior film* is 35.6 cm.; one-half of this would be 17.8 cm. The hair line on the slide (Fig. 1) is placed over 17.8 on line 0. On line 12 the corrected half perimeter is read as 14.8 cm. This is doubled to get 29.6 cm. as the total perimeter for the anteroposterior view.

The corrected perimeter values obtained from the lateral and anteroposterior views are averaged to obtain the *average fetal head circumference*. Two centimeters is usually added to this value to allow for the thickness of the fetal scalp. The pelvimeter is turned over, and the volume corresponding to the average circumference is read from the table on the back.

If the head is in a true anteroposterior or transverse plane, the cardinal fetal head measurements (the suboccipito-bregmatic, bi-parietal, and occipito-frontal diameters) can be obtained, the correction factors for these being identical to those used for obtaining the corrected perimeter in each view.

## CONCLUSIONS

A simple pelvimeter has been presented and the method of using it with the triangulation method of pelvimetry is discussed. This represents a simplification of the Snow method. The use of this pelvimeter has resulted in considerable time saving and increased accuracy by elimination of some steps in the usual method of correcting pelvic diameters and the fetal head measurements. In addition to these advantages, *wet film readings* of pelvic diameters are readily obtained, since the readings are made directly from the films with the use of this pelvimeter.

NOTE: The writer wishes to express his thanks to Ray A. Carter, M.D., Chief Radiologist, Los Angeles County General Hospital, for his suggestions and to Mr. Gerad Liefchild, R.T., Chief Technician, Department of Radiology, Los Angeles County General Hospital.

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## SUMARIO

### Sencillo Pelvimetro para la Pelvimetria Triangular

Descríbese un pelvímetro sencillo, explicándose la técnica para emplearlo con el método de triangulación en pelvimetría, lo cual representa una simplificación del método de Snow. El empleo de este pelvímetro ahorra considerable tiempo y acrecienta la exactitud por eliminar algunos pasos de la técnica corriente de rectificar las mediciones de los diámetros de la pelvis y la cabeza del feto. Además de estas ventajas, permite hacer fácilmente lecturas de los diámetros pelvianos en la película húmeda, en la cual se hacen directamente con este pelvímetro.

# EDITORIAL

## Radiology and the Practice of Medicine

**Presidential Address, Thirty-Third Annual Meeting**
**Radiological Society of North America[1]**

IN THESE DAYS of political confusion and, indeed, of confusion of thought generally, it is not surprising to find the practice of radiology, if not misrepresented, at least misunderstood. The complexities of modern social and economic forces have magnified the problems created by the phenomenal advancement of this specialty and rendered more urgent the question of its role and status in modern medicine.

Generically, radiology is defined as the science of radiant energy and radiant substances. Specifically, as it applies in the practice of medicine, it may be defined as the science and art of application of radiant energy and radioactive substances in the diagnosis and treatment of disease.

My thesis is a simple one. Is the practice of radiology the practice of medicine? If the answer is in the affirmative, what should be the relation of radiology to the patient, the hospital, and medical service plans?

Some states apparently attempt to define the practice of medicine by statute. Others provide in substance that no one shall practice medicine without a license and have left the matter of definition to the courts. The Supreme Court of Rhode Island has stated that "the 'practice of medicine' as ordinarily or popularly understood has relation to the art of preventing, curing or alleviating disease or pain. It rests largely in the sciences of anatomy, physiology and hygiene. It requires a knowledge of disease, its origin, its anatomical and physiological features and its causative relations; and, further, it requires a knowledge of drugs, their preparation and action. Popularly, it consists in the discovery of the cause and nature of disease, and the administration of remedies or the prescribing of treatment therefor."

The law provides that a person practises medicine within the meaning of that act who holds himself out as being able to diagnose, treat, operate or prescribe for any human disease, pain, injury, deformity, or physical condition. It further provides that no person shall practise medicine unless registered or licensed as therein provided.

Similarly, the highest court of Texas has held that "the 'practice of medicine,' as contemplated and defined by law, is not restricted to treatment of diseases and disorders of the human body by use of drugs or surgery."

It is clear that before one may hold himself out as a radiologist he must be licensed to practise medicine, since the tools of his specialty are employed to diagnose and treat disease, the very essence of the practice of medicine. For some years this was reversible. No longer does the mere possession of radium or x-ray apparatus qualify one as a radiologist.

In 1925, the American Medical Association established a section of Radiology, and in 1931 the Council of that Association began the listing of approved radiologists. As a protection to the public, the profession in general, the radiologists themselves, representatives from the five nation-wide radiologic organizations, the Section on Radiology of the A. M. A., the American Roentgen Ray Society, the Radiological Society of North America, the American College of Radiology, and the American

[1] Delivered December 1, 1947, in Boston, Mass.

Radium Society met in Milwaukee in 1933 and agreed unanimously that a specialty Board in Radiology be established.

The American Board of Radiology was incorporated, organized, and held its first meeting in Washington, D. C., in May 1934 and was accepted for membership in the Advisory Board for Medical Specialties and approved by the Council on Medical Education and Hospitals of the A. M. A. The list of diplomates of the Board replaced the Council's list of approved radiologists and the latter was discontinued.

Among the expressed purposes of the Board are these: "To encourage the study and promote and regulate the practice of radiology" and "determine the competence of specialists in radiology." To each candidate who meets the requirements of the Board, a certificate is issued. This may take one of two forms: (1) a certificate to the effect that the applicant has been found qualified to practise radiology in all its branches; (2) a certificate to the effect that the applicant has been found qualified to practise radiology in one or more of the following special fields: (a) roentgenology; (b) diagnostic roentgenology; (c) therapeutic radiology.

Before qualifying for examination, each applicant is required to present evidence that he has met definite standards, among which, after the completion of an internship, shall be a period of special training in radiology of not less than three years in approved clinics, hospitals or dispensaries which shall comprise an active residency of not less than twenty-four months, with graduate training in pathology, radiation physics, and radiobiology.

It is noteworthy that the Board states: "Any radiologist who is practising radiology honorably and efficiently should have no difficulty in obtaining a certificate. This Board has been organized, not to prevent qualified radiologists from obtaining certificates but to assist them in becoming recognized in their communities as men competent to practise in the special field of radiology."

Since radiology then has reached the honorable status of a medical specialty, is it good sense to attempt to decry it as a hospital service, a laboratory service, or a mere ancillary service? That hospital management and certain medical service plans, in wishful thinking, call it any one or all of these, does not make it so.

By definition, a hospital is an institution in which patients are given medical or surgical care. It has never been contemplated as an agency which provides medical and surgical services. A laboratory is defined as a place devoted to experimental study in any science or a place where something is prepared or some operation performed. It is as logical to describe the operation done by a surgeon in the operating room as a laboratory service as to describe the functioning of the radiologist as such. If by ancillary service is meant auxiliary or helpful service applicable to any specialized field in medicine, radiology can accept the appellation. If the term is used, as it often is, to minimize the importance of radiology in the diagnosis and treatment of disease, it can well be left to our fellow practitioners for refutation.

Because so much radiology is practised in hospitals, custom has described it as a hospital service. The hospital administrator desires to have it remain such to enable him, among other things, to control the income from it. One argument often presented is that the hospital supplies the patient to the radiologist and, therefore, should control the fees, although the same argument is not offered when patients are rotated among the surgeons or medical staff.

Again, it is loosely said that the hospital radiologist has a monopoly. If by that is meant the exclusive control of a service that enables him to raise the price of the service materially above the price fixed by free competition, the argument falls of its own weight. Fees for radiology are established, like all other medical fees, at a level sufficient to give a conscientious and competent practitioner a fair income for the amount of work he can do and do well enough to give the patient his money's

worth. If one radiologist earns an inordinate sum from the net income of his practice in a hospital, then he is doing more work than one man can do well. Two, three or perhaps more qualified radiologists are required to assist him. The same applies to surgeons, internists, and other specialists.

The peripatetic radiologist who "reads" films at several hospitals, no matter how much deplored, will continue to flourish while we have 6,280 approved hospitals and only 2,477 certified radiologists.

Radiology—x-rays is the term sold to the public—has been used as a bait by so-called non-profit insurance companies to sell contracts. The "non-profit" character of these organizations is "window dressing," meaning only that no dividends are paid to stockholders. It does not mean that the company does not make a profit or pay very profitable salaries to its personnel. It does mean, however, that it pays no government taxes as against the regular insurance companies, which yearly pay millions.

The cost of x-ray services has been presented to the public as beyond the means of the average person. Forget for the moment the totalitarian theory that the State should care for us from the cradle to the grave. Let us look at the actual cost of radiological service in hospitals. Despite the overload of x-ray examinations resulting from medical service plans, in the period 1936 to 1945 the average patient day cost in hospitals increased from $4.62 to $6.14. During the same period, the costs for the average x-ray department per patient day increased only 2 cents, from 21 cents to 23 cents. These figures come from a recently published survey made by the Division of Rural Health of the Commonwealth Fund.

Consider now the cost of radiology in some medical service plans. Here, the figure varies according to the benefits offered. If the maximum is $15, the ratio of x-ray costs to other costs will be less than if the maximum is $35 or if there is no maximum limit whatever. In the Michigan Medical Service Plan (which is largely a surgical care plan) diagnostic x-ray services up to $15 per year are included among benefits. Last year, 18.4 per cent of the 840,000 subscribers received x-ray services. Of total payments to physicians, 5 per cent was for x-ray services. The cost per subscriber per year for x-ray services amounted to twenty-nine cents.

Group Hospital Service of Delaware covers both surgical benefits and hospitalization. Diagnostic x-ray services are included up to $15 per year. Last year 30 per cent of the subscribers received x-ray services, and 10 per cent of all payments made to physicians was for x-ray services.

In California Physicians Service, x-ray examinations are covered for surgical cases, without any maximum. For the last recorded year, 18 per cent of the premium income was expended for diagnostic x-ray services.

These figures do not sustain the contention that radiology is a substantial part of hospital costs or that, under medical service plans, radiological charges are inordinate. In truth, for the most part, the radiological work done in hospitals, under medical service plans that require hospitalization, could be performed in the private office of the radiologist just as efficiently and without prejudice to properly operated medical service plans.

In certain hospitals, there have been deliberate efforts to increase the number of ambulatory patients in the outpatient service of the x-ray department for the frank purpose of increasing the hospital's profits from services rendered by the radiologist. This trend has not affected radiologists only. Except for city institutions, the charitable hospital is no longer with us. Indeed, "charitable" was taken out of the incorporated name of one Boston hospital. Outpatient departments in competition with the general practitioner, charging $1.50 and $2.00 a visit, are common today. Pay clinics with fees of five, ten, and fifteen dollars compete with the internist in private practice.

Ironically enough, one hospital account-

ing consultant "has advised hospitals (in a report soon to be published) that those specialists who maintain a practice in an outside office in the same community are in competition with the hospital they serve." Like some other spokesmen for the organized hospital world, this writer has assumed that certain medical procedures are the natural and proper functions of the hospital.

The question once again presents itself: Shall hospital corporations be permitted to practise medicine and to realize a profit from the services rendered by licensed physicians in the hospital? We are concerned here with the legitimate and proper functions of hospitals in relation to the practice of medicine by licensed physicians. In this connection, we are particularly concerned with contractual arrangements between hospital corporations and licensed physicians who practise in the hospitals owned and operated by such corporations.

Two clearly defined questions of law present themselves in a consideration of the practice of medicine in or by hospitals: (1) Is an incorporated hospital which employs a physician on a salary or other stipulated compensation, the corporation itself charging and collecting fees for the physician's services, engaged in the practice of medicine? (2) If the answer to the first question is affirmative, is such practice unlawful?

These questions have been the subject of considerable debate in medical and hospital circles. In a long line of cases, the courts have answered the two hypothetical questions set forth above in the affirmative.[2]

Some hospital spokesmen seek to brush this aside by saying that the physicians themselves are licensed and it is they who perform the actual services, not the hospital. But the courts have made no such distinction. A corporation which acts through salaried agents acts itself. This doctrine is so firmly settled in our jurisprudence that it is expressed by a Latin maxim: *Qui facit per alium, facit per se.*

Another rationale has been advanced by those who would justify the practice of medicine by hospitals. They contend that charitable hospitals are exempt from the prohibitions of the medical practice act. This is a question that has never been precisely adjudicated. We can rest upon the fact that so far the courts have made no distinction between corporations for profit and those not for profit when interpreting statutes regulating the practice of medicine.

The validity of the principles of the medical profession, however, are not based solely upon the law. These principles were erected to preserve the highest standards of medical practice and to protect the welfare of the patient. Among other things, they require that no third party, individual or corporation, shall be interjected between the patient and the attending physician or specialist who renders service to him.

In a long series of resolutions adopted by the House of Delegates of the American Medical Association over a period of many years, the objections of the medical profession to the tendency for hospitals to engage in the practice of medicine have been forcibly stated. Typical is the following, adopted by the House of Delegates at its annual meeting in 1942:

"WHEREAS, Evidence of continued encroachment of hospitals into practice of medicine are manifest in numerous group hospitalization plans which offer certain medical services on a service basis as a part of hospital care and in plans adopted by numerous hospitals which include certain medical services in an 'all inclusive' per diem rate for hospital care; now therefore be it

"RESOLVED, That the House of Delegates reaffirms the principles enunciated in official resolutions over a period of many years opposing the practice of medicine by corporations or the interjection of a third party into the personal relationship and financial transaction between doctors and patients; and be it further

"RESOLVED, That hospital corporations should not be permitted to engage in the practice of medicine through the medium of employed physicians or to enter into contracts with any individual, group or

[2] See Bulletin of the Inter-Society Committee for Radiology: The Employment of Physicians by Hospitals, by Mac F. Cahal. Radiology **37:** 237, 377, 507, 1941.

agency whereby the hospital agrees to furnish any medical services; and be it further

"RESOLVED, That, to the end that hospitals be discouraged from offering the services of licensed physicians to patients on a contract or service basis, all fees for medical services rendered in hospitals should be collected by or on the account of the physician rendering such service, and all physicians concerned in the care of a patient should give or send directly to the patient or other responsible party a statement, showing charges for professional services rendered, provided, however, that an exception to the foregoing principles may be made in the case of a formally organized partnership of physicians which acts in the capacity of an individual; and be it further

"RESOLVED, That the definitions of medical service and hospital service as applied to the principles stated herein shall be consistent with those applied in previous declarations of the House of Delegates in which medical services are construed as the services rendered by licensed practitioners of medicine, and hospital service as limited to hospital accommodations such as bed, operating room, medicines, surgical dressings, and general nursing care; and be it further

"RESOLVED, That the Board of Trustees be urged to proceed to the clarification of these problems as requested by the House of Delegates at its last annual session."

The following resolutions were adopted by the House of Delegates of the Association at its annual session in June 1947 and sent to all hospitals on the approved list of the Council on Medical Education and Hospitals:

"RESOLVED, That the House of Delegates of the American Medical Association is in complete agreement with the recommendations of the West Virginia State Medical Association in its opposition to the encroachment by hospitals and other organizations on the private practice of medicine; and be it further

"RESOLVED, That all fees for medical services be set by and collected by or for doctors of medicine rendering this service, and that all policies and practices involving medical services be approved by the medical board or medical staff before being put into effect; and be it further

"RESOLVED, That the Council on Medical Education and Hospitals recommend strongly that all hospitals conform to these resolutions; and be it further

"RESOLVED, That the House of Delegates of the American Medical Association go on record as strongly disapproving this practice of encroachment, and that notice of this action be sent to the American Protestant and Catholic hospital associations and to the Blue Cross organizations."

We must recognize, and grant, that the practical application of these principles established by law and by resolution of the medical profession raises difficult and complex questions. These questions can be settled, however, to the benefit of the patient's welfare—which is of course paramount—if the two parties involved, physicians and hospitals, will approach the issue with a tolerant and co-operative view. This has been attempted here in Massachusetts.

A committee representing the Massachusetts Hospital Service, the Massachusetts Medical Service, the Massachusetts Hospital Association, the specialties of radiology, pathology, anesthesiology, and the Massachusetts Medical Society met around the conference table this past Summer and reported as follows:

"This committee has been asked to define hospital services and medical services and to establish the proper relations between physicians and hospitals.

"In attempting its task the committee is well aware of the fact that conditions may properly vary in different localities and in different institutions, that the practice of medicine is undergoing rapid changes under unusual stresses, and that the concepts of tomorrow may vary markedly from those of today.

"There are, however, certain fundamental principles that should not change if the profession of medicine is to discharge its obligation to society on an increasingly high level.

"First, we accept the principle that the primary object of medical practice is to deliver the best possible care to the patient. Second, we believe that this objective can best be attained by an independent and unfettered profession, conscious of its ideals and its responsibilities.

"These principles are basically defined in Chapter III, Article VI, Section 5, of the Principles of Medical Ethics of the American Medical Association.

"It is unprofessional for a physician to dispose of his professional attainments or services to any lay body, organization, group or individual, by whatever name called, or however organized, under terms or conditions which permit a direct profit from the fees, salary or compensation received to accrue to the lay body or individual employing him. Such a procedure is beneath the dignity of professional practice, is unfair competition with the profession at large, is harmful alike to the profession of medicine and the welfare of the people, and is against sound public policy.

"Nothing in this report refers to interns, residents, or fellows. The committee is aware that his problem deserves separate consideration.

"In accordance with these principles your committee submits the following definitions and recommendations:

*I. Services Rendered in Hospitals*

"A. Non-Medical Hospital Services

"Non-medical hospital services are defined as those services, technical and non-technical, provided by other than a registered physician, which are required for the care of the patients, the making of a diagnosis and the treatment and prevention of disease; and those services rendered by a registered physician in an administrative capacity or as the head of a department when such services do not include the obtaining or interpretation of information in behalf of an individual patient.

"These shall be considered to include the following:

1. Administration.
2. Nursing.
3. Social Service.
4. Record Room and Library.
5. Pharmacy.
6. Dietary Service.
7. Housekeeping and Laundry.
8. Maintenance of building and grounds, including the provision, maintenance, repair and replacement of technical equipment and supplies.
9. Provision of technical and non-technical personnel and their qualified supervision.
10. Reports without interpretation from the clinical laboratories.
11. Such other service as may be necessary for the operation of a hospital.

"B. Medical Hospital Services.

"Medical hospital services are defined as those services other than administrative, rendered by a registered physician directly or indirectly to or in behalf of an individual patient for the obtainment and interpretation of data, including consultation and advice, for the diagnosis, treatment and prevention of disease. Such services will embrace the general and special practice of medicine, surgery, and obstetrics, and the practice of the related specialties including anesthesiology, physical medicine, radiology, pathology and clinical pathology including bacteriology, clinical chemistry and other clinical laboratory specialties.

"It is accepted as a basic principle of good medical practice that a professional interpretation should accompany the report on radiological examinations and on materials and tissues examined by the pathologist.

*II. The Establishment of Proper Relations Between Physicians and Hospitals*

"To establish principles governing the proper relations between physicians and hospitals, your committee makes the following recommendations:

"1. That the medical costs of hospital care be separated from the non-medical costs, as can be done by existing and accepted methods of cost-accounting, and that they appear thus separated on the statement submitted to the patient.

"2. That bills for all medical services be rendered in the name of the physician or physicians performing the services.

"3. That a basic principle in the establishment of charges should be that each department be self-supporting. This principle should be so applied that neither the hospital nor the physician rendering the service will exploit the patient or each other.

"4. That fees for medical services which are collected by the hospital be established by joint action of a representative committee of the staff and the governing body of the hospital and including also the head of the department and the administrator.

"5. That the basis of financial arrangement between hospital and physician may be salary, commission, fees, or such other method as will best meet the local situation, with due regard to the needs of the patient, the community, the hospital, and the physician.

"It is the opinion of the committee that acceptance and practice of these principles will clarify the confusion that now exists regarding responsibility for the payment of medical hospital services and non-medical hospital services, as defined above, by prepayment and other insurance plans."

This report of the committee to study special services was submitted to the Council of the Massachusetts Medical Society and unanimously adopted. Inasmuch as representatives of the Massachusetts Hospital Association, the Blue Cross and Blue Shield aided in the formulation of these principles and signed the report to the Council, it is anticipated that with the adoption of the report by the Council every reasonable effort will be made on the part of hospitals and medical service plans to implement its recommendations.

In recent years especially, we have heard of the socialization of industry, of finance, and of medicine. Socialization is a leveling process. It takes from those who have to give to those who have not. Governments do it by taxation. Individuals and corporations whose activities show profits are taxed and the taxes are applied to running the government, particularly to doing things for those who cannot do for themselves. This has resulted in business interests being unable to keep the profits they feel they have justly earned by their labors. There has been much bewailing on the part

of business men over the injustice of this. These men tell us that the American way of life is threatened, that in depriving private enterprise of the profit-motive the stimulation which built this country is being destroyed. There is truth in this.

But the very men who as financiers and industrialists oppose governmental socialization, as laymen on Boards of Trustees and managers of hospitals, medical schools and insurance schemes, blindly or not, attempt to apply to medicine the principles they condemn in their own particular sphere of activity.

In his new book, "Ghandi and Stalin," Louis Fischer contrasts the two personalities, the one a spiritual force, the other an autocrat. The author dwells on the evil of concentrated authority. How to curb power is the basic problem of human relationships. He points out that great concentrations of capital may threaten the liberties of the people but the transfer of all power from capitalists to government results in an unassailable despot. We do not want either.

We are truly living in an era of political romanticism, as exemplified by our left wing individuals who call themselves liberals. As Thomas Woodlock says, they fight under the banner of liberty. Yet, they are all at heart, consciously or unconsciously, for the totalitarian state, which is liberty's most deadly enemy. They are all for justice; yet, who are more unfair in their concepts of what is just?

Read the story of the Spartan state under Lycurgus, as related by Plutarch, to realize that totalitarianism did not begin with Hitler. Let us hope it will end with Stalin.

The socialization of medicine is part and parcel of totalitarianism. Granting that changes in the economics and technics of medicine may lead to changes in the functions of hospitals, there can be no compromise on one fundamental principle. Doctors must not become pawns in an autocratic nation-wide plan envisaged either by government or by hospital or insurance associations.

FREDERICK W. O'BRIEN, M.D.

# ANNOUNCEMENTS AND BOOK REVIEWS

## SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

The radiologists of Great Britain, through their National Radiological Committee, have invited the Sixth International Congress to meet in London in the year 1950. The invitation has been accepted by the International Executive Committee and the Congress will be held either in July or September of that year, the exact date to be determined later.

Dr. Ralston Paterson of Manchester, England, will be the President of the Congress.

## JOINT SCIENTIFIC SESSION, SECTIONS ON RADIOLOGY AND PREVENTIVE AND INDUSTRIAL MEDICINE AND PUBLIC HEALTH, A.M.A.

The Section on Radiology and the Section on Preventive Medicine and Public Health of the American Medical Association will hold a joint scientific session on June 25, in Chicago. This will be in the form of a symposium by clinicians and chemists who have been especially interested in the diagnosis, treatment, and prevention of pulmonary lesions occurring in workers in certain industries.

Pulmonary affections of occupational origin have interested the radiologist for many years. Likewise, for many years, it has been held that the only substances apt to produce a disabling fibrosis were silica and asbestos. It was especially felt that practically all silicates were relatively inert. Recently, however, it has come to light that peculiar pulmonary lesions have occurred among bauxite workers, diatomaceous earth workers, and among those exposed to beryllium or its acid radicals.

In order to bring the latest information regarding these from experienced radiologists, clinicians, and pathologists, the Section on Industrial Medicine of the American Medical Association has invited the Section on Radiology to a joint session. The purpose of this notice is to call this to your attention, for it portends an extraordinary symposium.

R. T. JOHNSTONE, M.D.,
Secretary, Section on Preventive and Industrial Medicine and Public Health

U. V. PORTMANN, M.D.,
Secretary, Section on Radiology

## THE AMERICAN RADIUM SOCIETY

A program of unusual interest is promised for the annual meeting of the American Radium Society for June 20–22, 1948, at the Hotel Stevens, Chicago. The Program Committee has invited a number of foreign guests who will report on recent advances in European radiotherapy, which information was inaccessible to Americans during the war years. The following have already promised to present reports on radium and x-ray treatment of cancer: Francois Baclesse and Juliette Baud of the Curie Foundation, Paris, the former in charge of roentgen therapy, the latter of radium therapy; Ellis Berven, Professor of Radiotherapy at the University of Stockholm and director of the Radiumhemmet; Sir Stanford Cade of London, who has written a most informative book on Radium and Cancer; Brian Windeyer, Professor of Radiotherapy at the University of London, and director of the Meyerstein Institute of Radiotherapy of the Middlesex Hospital, London; Constance Wood, Director of Radiotherapeutic Research Unit of the British Medical Research Council, in charge of Radium Beam; Dr. R. McWhirter, Director of Radiology, Royal Infirmary, Edinburgh, Scotland, who has treated 2,500 patients with cancer of the breast with local mastectomy and postoperative x-ray therapy. A number of equally eminent American radiotherapists will participate. An oration on the discovery of radium will be delivered by Dr. Edith Quimby at the banquet. The Janeway Lecture, Monday afternoon, on the "Achievement of Radium in the Fight Against Cancer," will be given by Sir Stanford Cade. Panel discussions on the treatment of cancer of the tongue, cancer of the breast and "Should Radiotherapy Be Separated from X-ray Diagnosis," as well as individual papers, will be given Monday and Tuesday. Special Refresher Courses will be conducted by the foreign guests Sunday morning preceding the regular sessions.

Those interested will find it advantageous to write immediately to Stevens Hotel, Chicago, Ill., for reservations and to Dr. Maurice Lenz, Chairman Program Committee, 840 Park Avenue, New York 21, N. Y., for further information regarding Refresher Courses.

## AMERICAN BOARD OF RADIOLOGY

Heretofore the American Board of Radiology has demanded that all candidates admitted to examination should be graduates of an approved Class A medical school. The Board has recently ruled, however, that those who have graduated from foreign and substandard medical schools before 1947 may be admitted to the examination if and when they have complied with the other requirements of the Board. No candidate who graduates from a substandard school (foreign or domestic) after 1947 will be admitted to the examination.

The Board has also ruled that a maximum credit of six months toward the required three years training may be allowed for formal didactic courses in the basic sciences.

Many candidates who have applied for the entire

field of Radiology or Roentgenology and who pass the examination in Diagnostic Roentgenology, or possibly in Therapy, ask for a limited certificate in the field in which they have passed, expecting to re-apply shortly for re-examination in the other field. This they are entitled to do, but in order to discourage candidates taking partial certificates, the Board has ruled that two years must elapse after a candidate accepts a certificate in one field before he may apply for additional certification.

### LOUISVILLE RADIOLOGICAL SOCIETY

At the December meeting of the Louisville Radiological Society, Dr. Joseph C. Bell was elected Chairman of the Society and Dr. Everett L. Pirkey was re-elected Secretary and Treasurer.

Dr. Bell also assumed, in January, the office of President of the Jefferson County (Kentucky) Medical Society.

### XIMIE RICHARD HYDE HONORED

Dr. Ximie R. Hyde, a member of the Radiological Society of North America, has recently assumed office as president of the Tarant County (Texas) Medical Society. He is a past president of the Texas Radiological Society.

### NATIONAL ADVISORY CANCER COUNC IL

The appointment of two of the country's leading men of science to the National Advisory Cancer Council of the National Cancer Institute, U. S. Public Health Service, was recently announced. The new members of the Council are Dr. Edward A. Doisy of the St. Louis University School of Medicine and a Nobel Prize winner in Medicine in 1943, and Dr. John J. Morton, Jr., of the University of Rochester (New York) School of Medicine and Dentistry.

Present members of the Council are Dr. Charles Huggins of the University of Chicago School of Medicine, Dr. Robert S. Stone of the University of California, Department of Radiology, Dr. Shields Warren of the Harvard Medical School, and Dr. Waltman Walters of the Mayo Clinic and the University of Minnesota School of Medicine. Dr. A. C. Ivy, who is Vice-President of the University of Illinois, is Executive Director of the Council. Dr. Thomas Parran, Surgeon General, U. S. Public Health Service, acts as Chairman.

### APPOINTMENT OF OFFICERS IN THE MEDICAL CORPS OF THE REGULAR NAVY

The statutory authority contained in Public Law 365—80th Congress, Title II (Army-Navy-Public Health Service Medical Officer Procurement Act of 1947) now makes it possible for civilian doctors to become commissioned officers in the regular Navy, provided they meet the professional and physical qualifications. This law for the first time does away with the age limitation of thirty-two years and permits doctors in civilian practice to enter the Navy and be commissioned with rank up to and including Captain. The law considers all strata of the medical profession, interns, residents, reserves, former medical officers who have resigned, and present practising physicians.

In order to make application, a doctor must be a citizen of the United States, a graduate of a Class A medical school, and have served at least one year's internship in an approved hospital. Candidates will then be judged on a number of qualifications, such as membership in a specialty board, teaching connections, number of years of professional or scientific practice, hospital or laboratory connections, military service, etc. The allocation of rank to successful candidates will depend upon their academic age, professional standing, and experience in the medical field. They will be eligible for promotion along with their fellow officers of equal rank.

Men who are interested should write to the Bureau of Naval Personnel, *via* the Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

### GENERAL ELECTRIC X-RAY CORPORATION

Of interest to radiologists will be the announcement by the General Electric X-Ray Corporation of the removal of its main offices, laboratories, and manufacturing plant from Chicago to 4855 West McGeoch Ave., Milwaukee, Wis.

## Books Received

Books received are acknowledged under this heading, and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

THE MEDICAL ANNUAL, 1947. A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX. Editors SIR HENRY TIDY, K.B.E., M.A., M.D. (Oxon.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. A volume of 464 pages with numerous illustrations reproduced from the papers reviewed. Published by John Wright & Sons Ltd., Bristol, and Simpkin Marshall (1941) Ltd., London.

## Book Reviews

DISEASES OF THE CHEST: WITH EMPHASIS ON X-RAY DIAGNOSIS: By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital and Country Sanatorium, New York; Visiting Physician in Tuberculosis and Physician-in-charge, Chest Clinic, Morrisania City Hospital, New York. A volume of 685 pages, with 355

illustrations (24 plates in color). W. B. Saunders Co., Philadelphia and London, 1947. Price $14.50.

Dr. Eli Rubin has written a book on *Diseases of the Chest* from the point of view of the modern clinician who realizes that such a work without strong emphasis on the roentgen aspects is of little value. His text is divided into six sections and these into numerous chapters.

Section I is composed of four chapters taking up, respectively, the fundamental aspects of anatomy as related to roentgenology, technical considerations of roentgenology, physiology, and symptoms and signs of lung disease. Section II includes six chapters, on the acute and chronic pneumonias. In dealing with these diseases, the clinical features relating to the etiology, pathology, symptoms and signs, and treatment are outlined, in addition to the roentgen signs. One chapter is devoted to chemotherapy. Section III, comprising eight chapters, is devoted to pulmonary tuberculosis. The clinical and roentgenologic aspects of the various types of tuberculous involvement are detailed; there is a chapter on complications, one on rest and pneumothorax, and one on surgical measures. The nine chapters making up Section IV describe chronic non-tuberculous diseases of the lungs and bronchi with special attention to bronchial obstruction. One chapter is devoted to pulmonary neoplasms. Section V (six chapters) covers diseases of the mediastinum, diaphragm, and pleura, and related structures, including heart-lung disease. One chapter is devoted to neoplasms of the mediastinum.

The principles of surgical treatment are discussed in Section VI (four chapters). This discussion, the work of Dr. Morris Rubin, is relatively general, to acquaint the reader with some of the possibilities of chest surgery without elaborate technical details.

The author states that the book is designed for use by general practitioners, sanatorium physicians, medical students, and radiologists. This last group will find, to their advantage, rather more clinical background material combined with the radiological aspects than is usual in purely radiologic texts. The book is recommended as a valuable addition to our present roentgen literature.

CHRONIC STRUCTURAL LOW BACKACHE DUE TO LOW-BACK STRUCTURAL DERANGEMENT. By R. A. ROBERTS, B.Sc., M.B., Ch.B., D.M.R.E. A volume of 105 pages, with 137 illustrations on 46 plates. Published by H. K. Lewis & Co., Ltd., London, 1947. Price 45s. net.

In *Chronic Structural Low Backache Due to Low-Back Structural Derangement* we have a monograph restricted to the consideration of chronic lumbar back pain of purely mechanical origin secondary to developmental anomalies or trauma or both. Attention is focused on the "pars interarticularis" or "isthmus" of the neural arch. This segment is described as a relatively delicate but structurally important pivotal center in motion between the vertebrae. It has been subjected to even greater stress by man's assumption of the erect position. Abnormalities are difficult to recognize roentgenographically unless oblique views in the standing position are taken.

Backache of the type under discussion is classified according to the nature and number of demonstrable radiologic findings, ranging from spondylolisthesis to ossification defects to no visible change at all.

In contrast to developmental anomalies and fractures of the "isthmus," the author describes a "strain deossification"—a different concept—wherein he postulates a demineralization instead of an eburnation resulting from abnormal stress or pressure. This results in relaxation of the supporting ligamentous structures and produces a "flail joint" or instability. It may be that one cannot accept immediately all of the ideas promulgated, but in the present day enthusiasm of the proponents of intervertebral disk injuries, this carefully prepared volume will make one pause before searching for a suspected protruded disk without objective corroborative evidence.

On the whole, the author presents a good case to support his contention. His plea for complete roentgenographic studies should be heeded by those who see and treat chronic back complaints.

Numerous illustrative case reports with a series of roentgenograms and well executed diagrams are presented. An extensive bibliography is included with references to works by anatomists, orthopedists and roentgenologists.

AN INTRODUCTION TO BIOCHEMISTRY. By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., Fellow of Trinity College, and Professor of Biochemistry, University of Dublin; Fellow of the Royal Institute of Chemistry; Member of the Royal Irish Academy. A volume of 569 pages. Published by Grune & Stratton, New York, 3d edition, 1947. Price $6.00.

Fearon's well known *Introduction to Biochemistry*, from Ireland, now appears in its third edition considerably revised and with several new sections consistent with the latest developments since 1940. Additional emphasis has been placed on subjects of special interest in clinical medicine, as, for example, acid-base balance, animal calorimetry, bone formation, food adsorption, detoxication, tissue chemistry, and nutrients. As a result, a tremendous amount of information is condensed into this single volume, well documented with the best series of general references to be found in any similar text. There is excellent writing, as is so frequently true of contributions from the British Isles.

The reader has somewhat of a sense of confusion, however, which is perhaps to be expected from the full coverage and condensation, in that the text is hardly adaptable for an elementary textbook be-

cause of certain advanced sections. Neither is it well adapted for advanced courses because much of the material is entirely too elementary and the book could hardly be considered sufficiently adequate for a definitive reference work. Several professors in biochemistry who have examined this text, at the request of the reviewer, have high praise for the effort and many parts of the presentation, but have generally expressed the feeling that it would be difficult to use in their University classes, particularly in many sections where the author plunges headlong into some of the most difficult and advanced modern technics. However, with this fresh point of view, the book undoubtedly can be used to advantage in conjunction with additional textbooks or reference volumes.

The printing appears to have been done by some sort of off-print method on only a fair grade of paper, and the rather flimsy binding easily gets out of shape. There are a number of errors, particularly in formulas, which have escaped the proofreader, as for example, in the table on page 245.

With the above mentioned reservations, it is very likely that this book will be a valuable addition to the library of biochemists and up-to-date teachers and research workers in clinical medicine.

SELECTED PAPERS FROM THE ROYAL CANCER HOSPITAL (FREE) AND THE CHESTER BEATTY RESEARCH INSTITUTE, London, Vol. IV, 1943–1944, comprising reprints of articles from various journals. A volume of 381 pages. Price 16/(£.16s.)

The selected papers published by the Staff of the Royal Cancer Hospital (Free) and the Chester Beatty Research Institute during the years of 1943 and 1944 cover a wide range of research and clinical work as seen in a cancer hospital and research laboratory, with abundant material on the physics of radiation as well as practical radiotherapy. There are also articles on diagnostic roentgenology. Many of the papers of radiologic interest have been abstracted in RADIOLOGY.

The papers making up the volume have been printed by the "replika process," furnishing an exact reproduction of the original text and illustrations. The paper is good and the binding of cloth is adequate for a book of this kind.

# RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

*Editor's Note:* Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates. Address: Howard P. Doub, M.D., The Henry Ford Hospital, Detroit 2, Mich.

## UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 607 Medical Arts Bldg., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, Mac F. Cahal, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

### Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Courtney S. Stickley, M.D., Bell Bldg. Montgomery. Next meeting at the time and place of the Alabama State Medical Association meeting.

### Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and annually at meeting of State Medical Society.

### California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, Sydney F. Thomas, M.D., Palo Alto Clinic, Palo Alto.

LOS ANGELES RADIOLOGICAL SOCIETY (A SECTION OF THE LOS ANGELES COUNTY MEDICAL ASSOCIATION). *Secretary*, Moris Horwitz, M.D., 2009 Wilshire Blvd., Los Angeles 5. Meets second Wednesday of each month at County Society Bldg.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 2000 Van Ness Ave. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Toland Hall, University of California Hospital.

### Colorado

DENVER RADIOLOGICAL CLUB. *Secretary*, Mark S. Donovan, M.D., 306 Majestic Bldg., Denver 2. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

### Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

### Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. A. Beals, M.D., St. Luke's Hospital, Jacksonville. Meets semiannually, in April, preceding the annual meeting of the Florida Medical Society, and in November.

### Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

### Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly as announced.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, John H. Gilmore, M.D., 720 N. Michigan Ave., Chicago 11.

### Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, J. A. Campbell, M.D., Indiana University Hospitals, Indianapolis 7. Annual meeting in May.

### Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

### Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney E. Johnson, M.D., 101 W. Chestnut St., Louisville.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

### Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday, 7:30 P.M.

**Maryland**

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, Harry A. Miller, 2452 Eutaw Place, Baltimore.

**Michigan**

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital, Detroit 1. Meetings first Thursday of each month from October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

**Minnesota**

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D., 802 Medical Arts Bldg., Minneapolis 2. Regular meetings in the Spring and Fall.

**Missouri**

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, Wm. M. Kitchen, M.D., 1010 Rialto Building, Kansas City 6, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday of each month, October to May.

**Nebraska**

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Ralph C. Moore, M.D., Nebraska Methodist Hospital, Omaha 3. Meetings third Wednesday of each month at 6 P.M. in either Omaha or Lincoln.

**New England**

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene, M.D., Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday at Boston Medical Library.

**New Hampshire**

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

**New Jersey**

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark as called.

**New York**

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway, L. I.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of every month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday evening each month, October to May, inclusive.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening each month at Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York 28.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary*, Murray P. George, M.D., 260 Crittenden Blvd., Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

**North Carolina**

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

**North Dakota**

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

**Ohio**

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Carroll Dundon, M.D., 2065 Adelbert Road, Cleveland 6. Next meeting at annual meeting of the State Medical Association, Cincinnati, March 31, 1948.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Edward T. Kirkendall, M.D., 700 North Park St., Columbus 8.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday, September to May.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

**Oklahoma**

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Peter M. Russo, M.D., 230 Osler Building, Oklahoma City. Meetings three times a year.

### Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Wm. Y. Burton, M.D., 242 Medical Arts Bldg., Portland 5. Meets monthly, on the second Wednesday, at 8:00 P.M., in the library of the University of Oregon Medical School.

### Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4, Wash. Meets annually in May.

### Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Arthur Finkelstein, M.D., Graduate Hospital, Philadelphia. Meets first Thursday of each month at 8:00 P.M., from October to May in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, R. P. Meader, M.D., 4002 Jenkins Arcade, Pittsburgh 22. Meets second Wednesday of each month at 6:30 P.M., October to June.

### Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., Lincoln Clinic, Lincoln, Nebr.

### South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

### Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

### Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month in Dallas in the odd months and in Fort Worth in the even months.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth 4. Next meeting Jan. 7–8, 1949.

### Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. Lowry Allen, M.D., Judge Bldg., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

UNIVERSITY OF UTAH RADIOLOGICAL CONFERENCE. *Secretary*, Henry H. Lerner, M.D. Meets first and third Thursdays, September to June, inclusive, at Salt Lake County General Hospital.

### Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., Norfolk General Hospital, Norfolk 7.

### Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Homer V. Hartzell, M.D., 310 Stimson Bldg., Seattle 1. Meetings fourth Monday October through May, at College Club, Seattle.

### Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, A. Melamed, M.D., 425 E. Wisconsin Ave., Milwaukee 2. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May and one day at annual meeting of State Medical Society in September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 to 5 P.M., September to May, inclusive, Room 301, Service Memorial Institute, 426 N. Charter St., Madison 6.

### Puerto Rico

ASOCIACION PUERTORRIQUEÑA DE RADIOLOGIA.—*Secretary*, Jesus Rivera Otero, M.D., Box 3524, Santurce, Puerto Rico.

## CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets on third Saturday of each month.

## CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

## MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Cosío, Marsella 11, México, D. F. Meetings first Monday of each month.

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## THE HEAD AND NECK

**The Three Types of Glioblastoma.** Eduard Busch and Erna Christensen. J. Neurosurg. **4:** 200–220, May 1947.

In a series of 133 glioblastomas, significant differences were found in macroscopic and microscopic pathology, in the age of the patient at admission, in the length of the history, in cerebral localization, and especially in the period of postoperative survival. The authors recognize three types of glioblastoma multiforme differing in the above-mentioned aspects and suggest the names glioblastoma angionecroticum, glioblastoma multicellulare, and glioblastoma magnocellulare. In most of the cases the preoperative diagnosis was glioblastoma, with the usual percentage of error (subdural hematoma, abscess, metastasis), but it was found impossible to make a reliable "type-diagnosis" on the clinical symptoms alone.

The only real help to a "type-diagnosis" has been cerebral angiography. Arteriovenous anastomoses were found in 21 of 33 angionecrotic glioblastomas, in only 1 of 24 multicellular tumors (and even then not quite typical), and in none of 17 patients with magnocellular glioblastoma. The investigation is of help when positive, but fails in a certain number of angionecrotic tumors, presumably because no anastomoses are patent at the time of angiography. The procedure has been of considerable assistance in making a decision as to operation in some patients whose general condition is poor. If anastomoses are seen, the tendency is to discourage surgery. The indication for operation, however, must in every case be an individual one. With experience, the differentiation of the three types can usually be made at operation. Several times in the series, however, a multicellular glioblastoma was taken to be angionecrotic, but the angionecrotic type was never taken for anything else. Glioblastomas of the magnocellular type have occasionally been mistaken for metastatic tumor, but are usually larger than the average metastasis.

In their first cases, the authors tried to carry out lobectomies, but they soon discontinued this procedure and made as clean an excision of the tumor alone as was possible without damaging important centers. The operative mortality for the whole series was 23.3 per cent. Of the patients who survived operation, all with angionecrotic glioblastoma were dead within a year and a half; nearly half of the multicellular and over half of the magnocellular groups were still living at the time of the report. Postoperative roentgen therapy was given in most cases (3600 r in 15 daily doses) and when possible the series was repeated after three and six months. While it is very difficult to judge the effect of radiation in these cases, the authors believe it is of definite value.

**Neurinomas of the Cerebellopontile Recess. A Clinical Study of One Hundred and Sixty Cases Including Operative Mortality and End Results.** Antonio Gonzalez Revilla. Bull. Johns Hopkins Hosp. **80:** 254–296, May 1947.

This is a study of 160 neurinomas of the cerebellopontile angle seen at operation in a period of twenty years (1926–45). Only the roentgen observations will be summarized here.

The great majority of the cases, 145, were unilateral acoustic neurinomas. In every case where the diagnosis of an acoustic tumor was suspected, stereoscopic films of the base of the skull were taken in an attempt to visualize the porus acousticus. Unfortunately, reports of the findings were available in only 114 cases. Of these, 52 (50 per cent) showed either enlargement or definite destruction of the internal auditory orifice, 7 merely showed evidence of increased intracranial pressure as manifested by destruction of the sella turcica and increase in the convolutional markings. Forty-five cases showed no abnormalities.

Air studies were rarely performed, being done in 8 cases where the diagnosis was in doubt. Ventriculography was used in all of them. In 5 of these the ventricles were markedly dilated, with definite evidence of a block at the aqueduct of Sylvius. In 1 case there was moderate dilatation of the ventricular system with no evidence of block or any other deformity. In 2 cases the ventriculograms were completely normal, showing small symmetrical ventricles with no evidence of obstruction. In none of these cases could the deformity of the ipsilateral horn as described by Stone and Schulze (Am. J. Roentgenol. **39:** 523, 1938) be demonstrated.

In the entire series there were only 3 cases of unilateral acoustic neurinoma with evidence of peripheral neurofibromatosis (1.8 per cent). In 2 of these cases x-ray studies showed marked destruction of the porus acousticus and in one they were negative. Air studies were not performed.

Roentgen examination of the skull was reported in 4 of the 6 cases of bilateral tumor of the nervus acousticus. In 1 there was evidence of erosion of the porus acousticus on both sides. Another showed unilateral erosion, and the remaining 2 showed no apparent change. There were no air studies performed in any of this group.

X-rays were taken in 2 of the 3 cases of neurinoma of the fifth nerve, and erosion at the porus acousticus was found in both.

Two cases of neurinoma of the tenth nerve were found in this series. In 1 patient, who showed widespread involvement of the cranial nerves, the authors were able to corroborate erosion of the porus acousticus.

**The Pneumoencephalogram of Cerebellar Atrophy.** J. P. Murphy and Roman Arana. Am. J. Roentgenol. **57:** 545–555, May 1947.

Detailed inspection of the encephalographic appearance of the contents of the posterior fossa is of greatest interest where degenerative disease or maldevelopment of the cerebellum is suspected. Air study of the brain, particularly in lateral views with the occipital region of the head superior, can reveal unexpected cerebellar disease, as well as confirm clinical impressions. Structural abnormalities of the cerebellum may or may not be associated with cerebellar symptomatology but, if the abnormalities are of sufficient magnitude, they may be visualized by pneumoencephalography.

Cerebellar atrophies may be subdivided as follows:

(A) Progressive degeneration (so-called "primary"), due to hereditary causes, intoxications, inflammatory processes, or unknown causes.

(B) Degeneration of the cerebellum secondary to disease of the pontile and olivary nuclei (olivoponto-

cerebellar atrophy), disease of the contralateral cerebral hemisphere ("crossed atrophy"), vascular disease. (C) Progressive cerebellar degeneration complicating Friedreich's ataxia, bulbar paralysis, peroneal muscular atrophy, epilepsy, feeblemindedness, etc.

Fifteen cases are presented. Four of these appear under the heading "primary degeneration or secondary (olivopontocerebellar) atrophy of the cerebellum," 2 are listed as secondary to or associated with cerebral atrophy, 2 as secondary to traumatic encephalopathy, and 3 associated with Friedreich's disease. In the remaining 4 cases hypoplasia (or secondary atrophy?) of the cerebellum was present in cerebral dysgenesis.

Cerebellar atrophy may be manifested by an enlargement of the cisterna magna and fourth ventricle, or by a widening and deepening of interfolial sulci and fissures, or a combination of these abnormalities. Scalloping and deep fissuring of the surfaces of the hemispheres and nodulation of the vermis are especially evident in cerebellar degeneration of the parenchymatous cortical or olivopontocerebellar types and in Friedreich's disease. Increase in size of the cisterna magna and fourth ventricle as compared with the normal is a feature of cerebellar hypoplasia.

CLARENCE E. WEAVER, M.D.

**Congenital Facial Paralysis.** J. P. Murphy and W. J. German. Arch. Neurol. & Psychiat. **57:** 358–361, March 1947.

Facial paralysis occurring in infancy and childhood may be acquired or congenital. The former is thought to be due to obstetric trauma, is almost always unilateral, and is not accompanied by paralysis of other cranial nerves. Congenital facial paralysis, on the other hand, is usually bilateral, and is almost always associated with paralysis of the abducens nerves. Since the first case was reported by von Graefe in 1880, some 60 examples have appeared in the literature. These were collected and discussed by Henderson (Brain **62:** 381, 1939). Many combinations of developmental defects accompanied the facial diplegia and paralysis of the abducens nerve in these cases. Pathologic examination was made in 4 instances, in 2 of which there was gross evidence of hypoplasia of the pons and medulla oblongata. It has been suggested that malformation of the cerebrospinal fluid system is responsible for the development of the condition.

The authors report a case of congenital facial paralysis associated with a multiplicity of developmental defects. Encephalographic examination disclosed enlargement of the basal cisterns. In addition, the horizontal distance from the ventral margin of the pons to the floor of the fourth ventricle was decreased from the normal, suggesting hypoplasia of the pons.

ANDREW K. BUTLER, M.D.
(University of Michigan)

**Calcification Occurring in the Eye.** P. B. English. M. J. Australia **1:** 549–551, May 3, 1947.

The literature on calcification in the eye is reviewed, and a case involving the sclera is presented, presumably the terminal stage of a post-inflammatory fibrosis. X-ray examination revealed extensive calcification of the posterior portion of the eye, extending forward into the lens. The eye was enucleated and microscopic study confirmed the roentgen findings. The films are reproduced.

**Evaluation of Diagnostic Methods Used in Cases of Maxillary Sinusitis, with a Comparative Study of Recent Therapeutic Agents Employed Locally.** Samuel Burtoff. Arch. Otolaryng. **45:** 516–542, May 1947.

One hundred patients were studied in an attempt to evaluate the accepted methods of diagnosing maxillary sinusitis. A history of recurrent or persistent head colds was given by the majority of patients. Objective methods of diagnosis included anterior rhinoscopy, transillumination, roentgenography, and exploratory irrigation. The erythrocyte sedimentation rate, the white blood cell count, and the differential count were recorded for each patient at the beginning and at the end of treatment. A vasoconstrictor, ephedrine 1 per cent in saline solution, was given for home use.

Anterior rhinoscopy revealed the presence or absence of pus. In 72 per cent of the cases studied, when pus was found in the middle meatus, along the middle third or posterior third of the inferior turbinate, it was also present in the antrum.

Transillumination did not prove an accurate diagnostic procedure. In 29 per cent of the cases, the antra appeared cloudy to hazy, while the antral return was clear following irrigation. In another 29 per cent the antra were clear to transillumination, while the antral return was filled with purulent secretion.

The roentgen diagnosis of maxillary sinusitis was confirmed in 86 per cent of the cases studied. At the first visit, a flat plate and one with a contrast medium—two-thirds poppyseed oil (40 per cent) and one-third cottonseed oil—were taken, and at the end of treatment, a third plate with a contrast medium. On the flat plate it is difficult to distinguish between a pathologic condition of the sinus due to excessive swelling of the mucosa, one due to a neoplasm, and one due to the accumulation of fluid; with a contrast medium, these distinctions can be made. Before taking a film with a contrast medium, saline irrigation was done to determine the presence of pus.

The erythrocyte sedimentation rate was high for all patients at the beginning of treatment, with a range of 18 to 50 mm. per hour. It decreased to normal as the condition improved. There was correlation between the sedimentation rate and the state of the antral return, and between the decrease in the sedimentation rate and improvement in the filling defect as seen roentgenographically.

Bacteriologic studies of the antral return were made to determine the most effective therapeutic agent. A non-bactericidal and non-bacteriostatic agent such as isotonic solution of sodium chloride, used locally, proved just as effective in bringing about the resolution of the sinusitis as did sulfathiazole and penicillin solutions, also used locally. Surgical intervention was recommended where there was no resolution with any of the solutions after as many as twenty-four to thirty antral lavages.

Twenty-four cases are presented in some detail.

**X-Ray Diagnosis of Cholesteatoma in the Temporal Bone.** Sölve Welin. Brit. J. Radiol. **20:** 192–201, May 1947.

In chronic otitis it is advisable to distinguish between cases with central perforations of the tympanum and those with marginal perforations, as cholesteatomas rarely occur in the former, but must be kept in mind in the latter. The clinical symptoms are not reliable in diagnosis, as they are variable.

Cholesteatoma cannot be diagnosed by x-ray until bone destruction has set in. When this has occurred, the first step is to take a combination of views of the temporal bone in various positions so that a complete anatomical picture may be obtained. Five projections are advocated:

(1) The patient supine, the chin drawn in, the central ray directed 35 degrees toward the feet (Towne's projection). This gives a symmetrical view of both sides, revealing slight differences in pneumatization, the degree of calcification of the cell walls, and the thickness of the cortical bone.

(2) The head in the lateral position; the central ray directed 15 degrees toward the feet. This view shows particularly clearly the cells around the antrum, in the tip, over the sinus, in the squamous portion, and at the sino-dural angle.

(3) The head lateral, the central ray directed 35 degrees toward the feet. This view shows the cells in the zygomatic root as well as those of the attic, aditus, and squama. Views (2) and (3) are taken stereoscopically.

(4) The head lateral, the central ray directed 5 to 10 degrees cranially and 30 degrees toward the face. This position demonstrates the condition of the cells in the petrous portion and reveals the diameter of the internal meatus.

(5) The standard submental-vertical view. This must be taken with the chin far enough extended so that the tympanic cavity and the external auditory canal are free of the mandibles. This view shows the presence or absence of exostoses in the external auditory canal and the condition of the ossicles.

The recognition of cholesteatoma is by no means easy, especially in the pneumatized mastoid. Only positive findings are significant. Typically the presence of cholesteatoma is indicated by an angular, polygonal or spherical area of destruction surrounded by a linear zone of calcified reaction. The changes may be found in any portion of the mastoid, depending upon the direction in which the growth has taken place. Thus a distinction is to be made between cholesteatoma of the external auditory canal, the attic, aditus, eustachian tube and antrum. Lesions in the attic may show enlargement of the aditus first. In the earliest cases, destruction of the posterior wall of the external auditory canal with enlargement of the aditus supports the diagnosis of cholesteatoma.

[In an earlier paper (Acta Radiologica **25:** 227, 1944. Abst. in Radiology **46:** 531, 1946) the author described his findings in a series of 109 cases of cholesteatoma in the temporal bone.] SYDNEY J. HAWLEY, M.D.

**On the Radiological Examination of the Eustachian Tube in Cases of Chronic Otitis.** Sölve Welin. Acta radiol. **28:** 95–103, Feb. 28, 1947.

The eustachian tube was filled with a contrast medium in 30 cases of chronic otitis and roentgenograms were taken in two projections: (*a*) a fully axial view with submento-vertically directed rays, and (*b*) a semi-axial view with parieto-occipitally directed rays. In most instances iodized oil, 10 and 40 per cent iodipin, was used, but a satisfactory density can also be obtained with the water-soluble 35 and 50 per cent solution. In 9 cases the author succeeded in demonstrating pathologic changes such as strictures, polyps, or inflammatory changes in the mucous membrane, thus securing anatomical explanations of the clinical findings.

## THE CHEST

**Roentgenological Aspects of Battle Injuries of the Chest.** Max Rakofsky and Victor P. Satinsky. Am. J. Roentgenol. **57:** 583–600, May 1947.

This report is based on approximately 200 cases of thoracic injuries observed at a base hospital. The importance of all the various positions used in roentgen study of the chest is discussed and the use of the over-penetrated film in identifying foreign bodies through massive pleural effusion is stressed. Roentgenoscopy is also valuable.

Postero-anterior and true lateral views are ordinarily sufficient to demonstrate and localize foreign bodies. Stereoscopy is particularly useful in localizing foreign bodies in intimate relationship to the thoracic cage.

Injury to the bony thorax is usually associated with pulmonary or pleural trauma. Pulmonary contusion is demonstrable roentgenologically as one or more areas of opacity of bizarre distribution and irregular outline. It resolves more slowly than blast injury or pneumonia.

Subcutaneous emphysema is readily shown, appearing as "streak-like" areas of increased radiolucency. It may be necessary to differentiate it from anaerobic infection.

Pneumothorax is frequently demonstrated. Tension pneumothorax due to a one-way valve type opening should be recognized and relieved.

Hemothorax appears in 75 per cent of battle casualties involving the chest. It is imperative to observe these cases closely, both clinically and by follow-up roentgen study. The well known signs of fluid, together with a history of trauma, presuppose the presence of blood. Generally it is present in association with pneumothorax. Occasionally it is loculated or encapsulated, in which case it may be represented by irregularly distributed fluid levels. In some instances an anteroposterior roentgenogram in the lateral recumbent position will prove useful in revealing loculations not demonstrable in routine views. Accurate localization is important in treatment by repeated thoracenteses. Clotted hemothorax may assume a variety of appearances, with mottling, multiple fluid levels, densely thickened pleurae or signs of traction.

Pleural sepsis occurs in approximately one-fifth of the cases. Infection is most frequently superimposed upon hemothoraces and pleural effusion. Lipiodol contrast studies are particularly useful for determining the size, extent, and position of empyema cavities and for evaluation of progress.

Bronchopleural fistula is an infrequent complication of chest wounds. It generally follows empyema, sinus tracts, or surgery. Lipiodol is used to demonstrate the fistula.

Blast injury is shown as streak-like bilateral symmetrical mottling.

Thoraco-abdominal wounds represent 10 per cent of battle injuries to the chest and have a 25 to 40 per cent mortality rate. Herniation of abdominal organs may follow. Subphrenic abscesses constitute an additional complication of transdiaphragmatic injuries.

Missile "tracks," demonstrable roentgenologically, are occasionally left in lung tissue. These may be solid or air-containing. The latter type may be mistaken for cavity or abscess.

Many illustrative cases are described and roentgenograms of the various conditions are shown.

CLARENCE E. WEAVER, M.D.

**Value of Tomography in Lesions of the Main Bronchi and Their Larger Sub-Divisions.** Stanley Nowell. Proc. Roy. Soc. Med. **40:** 399–404, May 1947.

Bronchial lesions must deform the lumen of the bronchus if they are to be demonstrated by radiologic methods. These deformities usually take the form of a smooth or irregular nodular narrowing; projection of a single nodule into the lumen; complete bronchial blockage, either V-shaped or rounded, or a blocking of the bronchus at its origin, with only a small nick showing. These effects may be caused by a large variety of lesions, both benign and malignant, intrinsic and extrinsic, and in the main bronchi and their larger divisions are readily visible on tomography.

The inflammatory type of intrinsic lesion is granulomatous, usually either tuberculous or syphilitic (gumma).

Intrinsic bronchial neoplasms usually give the appearance of a projecting nodule or bronchial obstruction. If a bronchus is not visualized, the examination should be repeated as the fault is usually a technical one. If, however, a bronchus is not seen and the adjacent bronchi show narrowing or deformity, then a definite block with invasion of adjacent radicles may be assumed. Neither tomography nor bronchoscopy may definitely distinguish an inflammatory from a neoplastic process, although suggestive evidence may be obtained. Thus, a single nodule is probably a neoplasm, benign or malignant; a complete V-block, especially at the origin of the bronchus, almost certainly indicates a carcinoma.

Extrinsic lesions include the lymphoblastomas and the benign mediastinal tumors. Both lymphosarcoma and Hodgkin's disease can invade the bronchi, causing a granulomatous occlusion and atelectasis. In such cases, the appearances are those of intrinsic invasion. Even the extent of invasion is no guide, as bronchial carcinoma may infiltrate widely. With malignant mediastinal tumors the invasion is usually more hazy and ill-defined, often with gross distortion of channels.

The author has found tomography useful in cases with clinical signs and symptoms suggestive of malignant growth but without atelectasis or mass shadows. Several cases with only slight hilar enlargement showed irregular narrowing of main bronchi, of proved neoplastic origin, on tomography. The value of tomography has also been demonstrated in cases of peripheral tumor shadows clear of the main bronchi. The author believes that a non-malignant tumor will displace neighboring bronchi. The bronchial segments running through a malignant growth are narrowed or occluded by invasion. Those adjacent to it are neither displaced nor narrowed. M. WENDELL DIETZ, M.D.

**Pulmonary Function Following Pneumothorax. An Investigation of the Volume and Ventilation of the Lungs.** Gösta Birath. Am. Rev. Tuberc. **55:** 349–365, April 1947.

In a detailed report the author discusses the results of a study to determine the effect on pulmonary function of so-called preventive pneumothorax in patients with pleurisy with effusion but without parenchymal lesions. Determination of pulmonary function after discontinuance of the pneumothorax revealed the following: (1) Total and vital capacities were diminished. (2) Equilibrium and residual capacities were not generally diminished to the same degree, and their share in the total capacity thus was increased. (3) Impairment of thoracic and diaphragmatic mobility as a result of pleural adhesions was responsible for these changes. Since serious impairment of lung function may result when lung contraction develops during pneumothorax treatment, it is suggested that the procedure should be abandoned if this complication appears likely to develop. L. W. PAUL, M.D.

**Community-Wide Chest X-ray Surveys. I. An Introduction to the Problem.** Francis J. Weber. Pub. Health Rep. **62:** 652–658, May 2, 1947.

Incorporated in this paper are the precepts of the chest x-ray survey in its wider aspects. Four major objectives are pointed out: (1) the discovery of every person in the country infected with tuberculosis; (2) isolation and medical care of every patient needing treatment; (3) after-care and rehabilitation; (4) protection of the afflicted family against economic distress. These widely divergent principles involve every component of community life.

Most of the community surveys so far undertaken have been of the short-term type, being completed within four to six weeks, but actually it would suffice to cover the same number of persons in two years or even longer, though any program geared so low that more than five years is required for its completion may be seriously questioned.

Two types of approach are considered: the campaign approach, which, including preliminary publicity and examinations, is measured in days or at most a few weeks, and the continuous program, which offers the advantage of joint planning by all community leaders and professional personnel. A combination of the two types is probably most advantageous, recurrent campaigns put on with a continuous campaign background. The organization of a community-wide x-ray survey should involve joint planning by (1) the official health departments, state and local, as well as other official agencies, such as welfare departments and vocational rehabilitation offices; (2) voluntary associations, state, local, and others, and (3) the medical profession. At the request of the state or local group, the U. S. Public Health Service is prepared to conduct a demonstration survey in suitable areas, furnishing the necessary equipment and personnel, but depending upon the state and local health departments for basic services, including clinical and follow-up facilities, and upon the community for the basic organizing necessary to bring the people out for examination. There are, however, certain requirements to be fulfilled. The area must be in definite need of solution of a particular problem. The local community must be prepared to follow up the demonstration adequately and must demonstrate a willingness to co-operate and continue to support a general health program, as well as this particular tuberculosis program.

In addition to the amount of time to be spent on actual case finding, the following points must be taken into consideration:

1. Number of units required for the work. A fully automatic unit with qualified personnel can expose and develop 500 x-ray films in an average working day, but a good daily average is 300 films.
2. Probable number of cases to be detected that will require treatment and follow-up.
3. Necessary facilities present in the community and other facilities that must be obtained—clinics, hospital beds, and health department facilities.

4. Facilities needed for follow-up. This will include estimates of medical, nursing, and record keeping requirements and of needed provisions for a continuous educational program with emphasis on the interpretation of the control work and the disease.

5. Number of personnel needed to carry out the work in the time prescribed.

The community-wide chest x-ray survey has been compared to the modern military campaign with respect to both tactics and objective. The analogy seems justified. Whatever we war against, we cannot expect victory if we resort to defense alone: we must attack. The objective, of course, is complete eradication of the disease. SYDNEY F. THOMAS, M.D.

**Technique of Chest Fluoroscopy.** L. Walk. Acta radiol. **28:** 14–16, Feb. 28, 1947.

The diagnostic results in chest fluoroscopy are determined not only by the clinical experience of the roentgenologist but also by his technic. Fluoroscopy has to visualize hidden lesions as well as to disclose typical aspects which cannot be shown by films in the prescribed positions. The author's technic involves three phases, with frequent rotation of the patient: (1) inspection of the diaphragm and the basal parts of the lungs; (2) inspection of the heart and the mediastinum and of the general configuration of the chest; (3) inspection of the lungs, especially the apices. Diagnostically valuable aspects found at fluoroscopy are fixed by spot films. Every exploration is completed by a standard roentgenogram of the chest, showing those finer structural alterations which cannot be seen fluoroscopically.

**Immobilization of Both Lungs Produced by the Equalizing Pressure Chamber with Results of Treatment in Pulmonary Tuberculosis.** Alvan L. Barach. Ann. Int. Med. **26:** 687–703, May 1947.

The author describes a modification of the "barospirator" devised by Thunberg in 1926 for artificial respiration in cases of respiratory paralysis due to poliomyelitis or morphine poisoning, whereby an equal pressure is simultaneously applied to the inner and outer surfaces of the chest wall, as well as to the upper and lower surfaces of the diaphragm. With this device a normal exchange of oxygen and carbon dioxide is maintained without the movements or effort of breathing.

Roentgenograms of the chest taken during the positive and negative phase of pressure on the same film, during residence in the equalizing pressure chamber, revealed no movement of the ribs or diaphragm. Not only does this type of local lung rest favor the process of healing by reducing changes in the physical state of tuberculous lesions, but absence of lung movement also may have a specific effect in collapsing those cavities in which a check-valve mechanism had been previously operating to keep the cavity inflated. This latter assumption is supported by the observation that one of the most striking effects of arrested lung movement has been the disappearance of cavity.

This type of local lung rest has been employed in 12 cases of advanced and moderately advanced tuberculosis over a period of nine years. Clinical recovery was obtained in 6, marked improvement in 1, slight to moderate temporary benefit in 3, and no change in 2. Patients have been treated from eight to eleven hours daily for a course arbitrarily set at three and one-half to four months. When marked clinical improvement has been initiated, the patient is allowed freedom from the chamber for a variable period of bed rest or convalescent care. Of the 12 patients, 1 has had three courses of treatment, 3 have had two courses, and 8 one course.

In 2 cases a clinical recovery followed a single course of treatment. A third patient, recently treated, is apparently obtaining an arrest of his disease, as indicated by negative sputum tests and clearing of infiltrative lesions in the lungs. Of the 3 patients receiving two courses, 2 became clinically well; the third showed conspicuous and marked improvement, with concentrate sputum and gastric tests repeatedly negative in the past four years. However, roentgenograms still reveal evidence of a small cavity at the site of an original large cavity.

The sequence of events in the case in which three courses were given indicates the specific effect of lung immobilization: (1) disappearance of the cavity in the right lung and decrease in size of cavity in left lung after the first course; (2) increase in size of cavity in left lung after six months modified bed rest; (3) collapse of cavity in left lung after second course; (4) re-expansion of cavity in left lung after one year's activity; (5) closure of cavity after third course, followed by clinical recovery and ability to work for four years.

In re-appraising the results in 2 patients in whom no diminution in the size of the cavity took place, the factors considered were (1) the possibility that the cavities were adherent to the chest wall over a wide area and (2) that continuous arrest of lung movement was not obtained, due to failure of adequate supervision.

STEPHEN N. TAGER, M.D.

**Pulmonary Tuberculosis Simulating Bronchogenic Carcinoma. A Report of Four Cases.** Anibal Roberto Valle and M. Lawrence White, Jr. Am. Rev. Tuberc. **55:** 449–456, May 1947.

Four cases are reported of pulmonary tuberculosis simulating bronchogenic carcinoma to the extent that surgical exploration of the lung was done. All of the patients had sputum examinations negative for tubercle bacilli and negative tuberculin tests. In three, the removed specimens showed frank tuberculosis. In the fourth, the lesion was chronic inflammatory in nature and was thought to be healed tuberculosis. In all of the cases the roentgenograms were suggestive of carcinoma. It is pointed out that the symptoms of cough, gradually becoming productive, small hemoptyses, chest pain, weight loss, and weakness are all common to bronchogenic carcinoma and tuberculosis or other chronic inflammatory disease. If orthodox methods of examination carefully and repeatedly applied fail to differentiate between these diseases, exploratory operation is justified. L. W. PAUL, M.D.

**Bronchiectasis Secondary to Primary Tuberculous Infection in Infancy.** T. Valledor. Rev. cubana pediat. **19:** 264–295, May 1947.

For ten years in the Pediatric Dispensary and in the Angel Aballi Anti-Tuberculosis Children's Sanitarium, a considerable number of cases of primary tuberculous infection have been systematically studied with bronchography, repeated in each case at intervals of from three months to a year. The objective was the search for secondary bronchial lesions and the obstructive bronchial factors in the pathogenesis of infiltrative and atelectatic forms of primary infection in children. Bronchoscopy was also done in a large number of cases.

One hundred cases of bronchiectasis secondary to tuberculous primary infection were selected for study. Secondary bronchiectasis is very frequent following tuberculous primary infection in children; in fact, it occurs in the majority of cases. The degree and importance of bronchial dilatation varies from a small, residual dry bronchiectasis to a large, wet bronchiectasis, which may progress to the point of crippling the patient. Most of these dilatations are due to bronchial obstructions caused by compression of enlarged lymph nodes, bronchial spasm, allergic edema of the mucosa, and accumulated secretions. The bronchial obstructions are followed by atelectasis, either lobar or segmentary. The obstruction may be total or partial; usually it is total only in the first transitory phase of the process. After a few days or weeks the bronchus becomes permeable and dilatations of the tributary branches become visible bronchographically. Bronchiectasis is of gradual development and gives bronchographic shadows of variable gradation, ranging from the aspect of bamboo cane, pea pod, etc., to the typical cylindrical ampullar and saccular dilatations.

One often sees very great displacement of the affected bronchial branches due to the atelectatic retraction, and in some cases to the compression of the obstructive emphysema of the neighboring zone. The bronchiectasis is usually localized in the right middle lobe, sites next in order of frequency being the right upper lobe, the left upper lobe, including the lingula, and the inferior lobes. Many of the residual bronchiectases are dry and give few or no symptoms at all, especially when located in the upper lobes. In the middle lobe, the lingula, or in the inferior lobes, especially when the atelectasis is chronic, there develops a syndrome of internal asymmetry. Anorexia occurs; there is cardiorespiratory insufficiency; morning expectoration is accentuated; finally hemoptysis, sometimes profuse, may develop.

JAMES T. CASE, M.D.

**Pulmonary Type of Tularæmia (Two Cases).** A. G. MacKinnon. Canad. M. A. J. **56:** 541–542, May 1947.

Two cases of the pulmonary type of tularemia from the Northwest Territories are presented. The patients were an Indian woman and her four-year-old son. Infested squirrels had been skinned in their one-room log cabin.

In the first case, the x-rays on admission showed bilateral density in the lungs, which was considered to be a pneumonic process, with possibly left-sided pleurisy. A subsequent film showed some residual mottling, but a repeat film later showed no definite evidence of pulmonary disease. In the second case, the x-rays showed increased density in the right chest, but not of a uniform nature. This was thought to be due to pockets of empyema, or possibly a pneumonic condition.

In these two cases there was no apparent "portal of entry" lesion. The lymph nodes were not noticeably enlarged.

DANIEL WILNER, M.D.

**Lung Changes Associated with the Manufacture of Alumina Abrasives.** Cecil Gordon Shaver and Andrew Rutherford Riddell. J. Indust. Hyg. & Toxicol. **29:** 145–157, May 1947.

The authors report a series of cases of lung disease developing in connection with the manufacture of an abrasive, the main ingredient of which is bauxite. The etiology is doubtful. The industrial process, which had previously been considered innocuous, involves exposure to high concentrations of alumina and silica, both in a very fine state of division, and to small quantities of many other substances. The disease is essentially an interstitial lung fibrosis, non-nodular in type. It may be rapidly progressive. Profound emphysema accompanies the invading fibrosis. Emphysematous blebs and bullae occur on the visceral pleura. These are apt to rupture spontaneously and give rise to pneumothoraces.

Of 344 individuals exposed in four different industrial plants, 35 showed definite radiological evidences of disease and 13 others lung changes classified as doubtful. In general, well established cases show a widening of the mediastinal shadow, which may partially obscure the shadows of the hili. As a rule, the diaphragm is irregular. It shows tenting and frequently is elevated. The distortions of the mediastinum and diaphragm become less marked or may disappear when pneumothorax occurs. Indeed, a mediastinal shift away from the side of extensive collapse is the rule. There is always bilateral shadowing in the lung fields. This is lace-like or granular in appearance. It is more pronounced in the upper halves of the fields and more intense toward the lung roots. It tends to shade off toward the periphery. Coarser shadowing throughout the lung fields is frequent in the more advanced cases. In these the lace-like quality tends to be lost. Emphysematous changes, indicated by large clear areas enclosed in ring-like shadows, also characterize the advanced cases. Very often this type of shadowing is more pronounced at the periphery of the lung fields. In one case a very definite bleb-like shadow was present on the pleural surface of the collapsed lung.

Evidence of fluid in association with pneumothorax was occasionally seen. This was not common, however, and showed no tendency to persist. Fluid was never diagnosed on physical examination. It is significant that in no case with pneumothorax did secondary infection in the pleural cavity develop. In none was there clear radiological evidence of complicating tuberculosis. Neither has follow-up demonstrated that tuberculosis was a factor in any case. Roentgenograms are reproduced to illustrate the changes which occurred over a period of three years in one patient.

The disease has been fatal in 7 instances. In several it has progressed rapidly and has produced serious disability. These cases most closely resemble some described in the German literature as a result of exposure to aluminum dust.

**Disseminated Ossified Nodules in the Lungs Associated with Mitral Stenosis.** A. Elkeles. Proc. Roy. Soc. Med. **40:** 405–408, May 1947.

The purpose of this paper is to emphasize a special type of pulmonary nodular calcification occasionally associated with mitral stenosis. The nodules were found to consist of true bone in cases of this type previously reported and in the two additional cases herein described. Evidence is produced indicating the probability that these lesions are the end-result of rheumatic pneumonitis and not the outcome of chronic passive congestion as hitherto believed.

Calcified miliary tuberculosis presents the greatest difficulty in differential diagnosis. Association of the calcifications with mitral stenosis should raise doubt as to their tuberculous character, for pulmonary tuberculosis, although a common complication in congenital

heart disease, is only rarely associated with mitral stenosis. The distinguishing features of the chest roentgenograms of the two conditions are as follows. In *mitral stenosis*, the calcified nodules vary from the size of a pinhead to that of a pea. They show various shades of density, are not always discrete, and have a tendency to coalesce. The nodules are distributed over the central as well as the peripheral lung fields. In *calcified miliary tuberculosis*, the calcifications are discrete and more uniform in size and density. They mainly involve the central lung fields. There is usually evidence of a primary or post-primary tuberculous lesion.

Calcified miliary nodules occur, also, in a number of other conditions, as pneumoconiosis, pneumomycosis, sarcoidosis, etc., but these may usually be differentiated on the basis of the history, clinical picture, and laboratory findings. Finally the calcifications of mitral stenosis are not to be confused with the miliary type of long-standing passive congestion also associated with that disease, due presumably to a combination of swollen end-on vessels and alveoli filled with heart-failure cells. M. WENDELL DIETZ, M.D.

**Mediastinal Tumors in Leukosis.** Jørgen Bichel. Acta radiol. **28:** 81–94, Feb. 28, 1947.

In the last fifteen years, 217 patients with leukosis were treated at the Radium Center for Jutland (Denmark). Fifty-three of the cases were chronic myeloid, 129 chronic lymphatic, and 22 acute leukosis; the rest (13) were either more uncommon forms or the diagnosis was uncertain. At the time of the report, 39 of the patients were still alive, 9 with chronic myeloid, 30 with chronic lymphatic leukosis.

Among the patients with acute leukosis, there were 4 in whom mediastinal tumors were found, probably arising from the thymus. In 2 of them, this tumor was the predominant symptom at admission. These 4 cases are reported in detail and discussed together with 114 cases from the literature.

The combination of tumor in the anterior portion of the mediastinum with a leukemic blood picture is most frequently seen in children, chiefly in boys. In most cases, the tumor seems to have been due to a proliferation of round cells in the thymus, but the histogenetic connection between these and the various thymic elements is not yet fully elucidated. In many cases the tumor appeared to be primary in relation to a subsequent generalization. Though it is doubtful if the cases of this type can rightly be considered as constituting a pathologic entity, essentially different on the one hand from leukoses and on the other from lymphosarcomas, the author thinks that there are good grounds for considering them, clinically, as a separate group.

It is possible that radiotherapy may in some cases hasten the development of the leukemic phase, but as a palliative measure cautious roentgen treatment is nevertheless of great value as a means of reducing the great severity of the symptoms caused by the presence of the large intrathoracic tumor, which often is extremely radiosensitive.

**Diagnostic Value of Roentgenography and Fluoroscopy in the Diagnosis of Rheumatic Heart Disease.** John B. Schwedel. Am. J. Med. **2:** 517–524, May 1947.

In a seminar on rheumatic fever, Schwedel discusses roentgenography and fluoroscopy of the heart in the diagnosis of rheumatic heart disease under the following headings (1) value in arriving at an etiological diagnosis, (2) estimation of the anatomical sites of lesions, (3) manifestations of rheumatic activity, (4) as an aid in estimating the age or duration of cardiac involvement, and (5) clinical correlation between signs and symptoms and their roentgenologic manifestations.

(1) There is no typical roentgen picture in rheumatic heart disease. In response to various kinds of damage there is cardiac enlargement involving one, two, or even all chambers. Enlargement of the left auricle and the right ventricle are frequently associated in mitral valve disease. It is the association of enlargement of the individual chambers that is suggestive, however, rather than the over-all shape of the heart.

(2) The size of the individual chambers is important and is determined chiefly by fluoroscopy, with confirmatory films in the postero-anterior and in the right and left anterior oblique positions.

(3) The appearance and regression of a pericardial effusion in patients with rheumatic heart disease are generally acknowledged as evidence of rheumatic activity. In the author's opinion, progressive cardiac enlargement or individual chamber enlargement, over previous findings, also indicates rheumatic activity even in the absence of congestive failure.

(4) Valvular or pericardial calcification is a late finding in rheumatic heart disease, never having been found by Schwedel before eight or ten years after the onset of the initial episode of rheumatic fever. Pulmonary fibrosis of the stippled variety, simulating miliary tuberculosis and at times silicosis, is a late sequel of chronic recurrent pulmonary congestion in patients with rheumatic mitral valvular disease. An interesting and an important aid in estimating the age of cardiac involvement is the finding of elevation and compression of the left main bronchus by an enlarged left auricle. Compression of the bronchus can occur only while the bronchial cartilage is soft and pliable, that is, not beyond the teens. Elevation of the left bronchus without compression may occur after that age.

(5) The roentgenologic pulmonary manifestations of rheumatic disease may be classified as follows: (1) pulmonary congestion, vascular and interstitial; (2) pleural effusions, general, loculated, and interlobar; (3) pulmonary infarction; (4) acute pulmonary edema; (5) chronic pulmonary edema; (6) rheumatic pneumonia; (7) pulmonary fibrosis; (8) pleural thickening.

**Direct Intracardiac Angiocardiography—Its Diagnostic Value.** Ignacio Chávez, Narno Dorbecker, and Alejandro Celis. Am. Heart J. **33:** 560–593, May 1947.

The authors describe their method of direct intracardiac angiocardiography using 50 to 90 c.c. of a 70 per cent diodrast solution. This is injected through a No. 12 or 14 rubber catheter, introduced into the heart through an exposed external jugular vein. The tip of the catheter is positioned under fluoroscopic control, either in the right auricle or the right ventricle as desired. The article is profusely illustrated and the authors describe the right and left heart and aorta as found in normal and abnormal states. In the presence of abnormal conditions the contrast substance may follow the normal circuit or may take an anomalous course, because of perforations, anomalous vessels, and shunts.

The authors claim the following advantages for this method: (1) it places the opaque substance where it is desired; (2) it immediately opacifies the part to be visualized; (3) the contrast substance is injected very rapidly, without dilution. Among the conditions in which it has been found useful is patent ductus arteriosus. While the duct cannot itself be visualized, a delayed back-flow filling of the pulmonary artery at the time that the aorta fills is a decisive radiologic sign.

HENRY K. TAYLOR, M.D.

**Congenital Aortic and Subaortic Stenosis with Associated Anomalies of the Aorta.** A. Grishman, M. F. Steinberg, and M. L. Sussman. M. Clin. North America **31:** 543–556, May 1947.

The authors' study of 23 cases of aortic and subaortic stenosis led them to the conclusion that this diagnosis should be considered whenever a loud, harsh systolic murmur is encountered in the right second space, over the mid sterum or at Erb's point. The presence of a soft diastolic murmur without peripheral signs of insufficiency does not exclude the diagnosis.

The need for careful palpation of the arterial pulses is particularly brought out. The systolic thrill and murmur were often recognizable in the innominate and carotid arteries. The configuration of the pulse tracings recorded over these vessels, however, was the most important diagnostic sign. The characteristic finding as revealed in these tracings was a slow initial rise, an anacrotic notch, systolic vibrations, and a systolic plateau. Electrocardiograms showed either normal or left axis deviation.

Roentgen examination revealed varying degrees of left ventricular enlargement. The ascending aorta often is prominent, with its convexity to the right increased. Marked dynamic pulsations are frequently noticed. Angiocardiography did not demonstrate the stenotic zone clearly, with the possible exception of one case, in which a definite infravalvular irregularity was seen. It is hoped that roentgen exposures made in predetermined phases of the cardiac cycle will assist in this demonstration.

Of great interest was the frequent finding of associated abnormalities of the aorta. The prominence of the ascending aorta seen by conventional roentgenography proved to be due to post-stenotic pulmonary artery dilatation, which occurs in about one-half of the cases of pulmonary stenosis. However, narrowing and angular deformity of the aortic isthmus were also encountered.

In the authors' opinion aortic and subaortic stenosis are not so commonly benign as is ordinarily thought.

**Coarctation of the Aorta: Clinical and Surgical Aspects.** Rodolfo Kreutzer, Angel D. Gonzalez Parente, and Alfonso R. Albanese. Rev. argent. de cardiol. **14:** 79–102 (May–June), 1947.

This is a lengthy discussion of the subject of aortic coarctation based upon 5 cases found among 8,000 children seen in the cardiologic clinic of the Hospital de Niños (Buenos Aires). The authors follow the classification of Bonnet, who in 1903 divided his cases into infantile and adult types, the former so named because the stenotic portion involves the entire isthmus of the aorta and is accompanied by serious cardiac malformations which bring about death shortly after birth. In the adult type, on the other hand, the coarctation is the only important anomaly and the stenosis is much less extensive—one centimeter or less. It is usually found at or just below the opening of the arteriovenous duct or of the arterial ligamentous structure remaining after its obliteration. The clinical importance and symptoms depend upon the degree of obstruction, in the discussion of which Abbott's classification is followed. Angiocardiography is recommended as permitting a precise diagnosis of the level and grade of the stenosis. It is recommended that in every pediatric examination the femoral and abdominal pulse should be routinely palpated and compared with the radial pulse. The electrocardiogram is valuable, showing left axis deviation, deep Q in lead 3, deep S in lead 1 and in all the precordial leads.

JAMES T. CASE, M.D.

**Coarctation of the Aorta: II. Clinical Features.** Crighton Bramwell. Brit. Heart J. **9:** 100–124, April 1947.

Twenty-six cases of coarctation of the aorta are reported. In 20 patients, the diagnosis was made clinically; in 5, roentgenologically; and in one at necropsy. The classification (Evans: Quart. J. Med. **2:** 1, 1933), clinical manifestations, and prognosis of the condition are discussed. The roentgen diagnosis is to be taken up in more detail in a subsequent paper.

**Traumatic Dissecting Aneurysm of the Aorta.** Djin-Yüan Guo. Acta radiol. **28:** 25–31, Feb. 28, 1947.

A case of dissecting aneurysm of the aortic arch following trauma to the chest is recorded, with radiologic findings over a period of years. The symptoms immediately following the injury (in 1935) subsided and the patient was thereafter in excellent health, with no cardiovascular complaints even during the strenuous period of military service. A routine roentgen examination in 1944 showed the presence of the aneurysm. The author regards this history of rapid regression of clinically threatening early symptoms and subsequent freedom from complaints as almost classic and believes that it probably accounts for the fact that the condition has been considered extremely rare.

**Unusual Longevity in Aneurysm of the Thoracic Aorta.** Ralph Kauntze. Brit. Heart J. **9:** 96–99, April 1947.

A case of aneurysm of the thoracic aorta of prolonged duration is recorded. The first symptoms referable to the aneurysm occurred in 1919, and in 1921 the lesion was sufficiently advanced to cause dysphagia and hemoptysis. The patient was given mercury inunctions, potassium iodide, and later five injections of novarsenobenzol, following which there was no further antisyphilitic treatment until September 1931. The hemoptysis recurred temporarily in 1934 and again in 1941. In 1946 the patient's condition was still reasonably good, though there was a sudden increase in the size of the aneurysm. X-ray examination showed calcified plaques in the aorta and in parts of the aneurysmal sac.

**The Radial Kymograph.** Mario Lenzi. Radiol. med. (Milan) **33:** 244–251, May 1947.

The author points out that the true kymographic record of a moving organ requires that the position of the slit coincide with the direction of the motion. Since many of the motions of the heart and great vessels occur

in radial directions, the author has built and used a kymograph with fixed radial slits and a rotating film, with excellent results. CESARE GIANTURCO, M.D.

## THE DIGESTIVE SYSTEM

**Unique Case of Foreign Body in the Esophagus.** Virgil J. Schwartz. Arch. Otolyarng **45:** 562–567, May 1947.

A case is presented in which a coin (a quarter) accidently swallowed by a seven-year-old boy passed through the esophageal entrance in the usual manner, but somehow made its way toward the extreme left of the esophagus and turned in an anteroposterior position, perhaps through striking the bulge of the arch of the aorta. Thus the posterior edge of the coin became wedged in an esophageal pocket beside the body of a vertebra, while the anterior edge was similarly wedged in a pocket to the left of the trachea. It is probable that downward escape was prevented by the left main bronchus, which leaves the trachea between the fourth and fifth thoracic vertebrae. Thus the coin was caught laterally by the distended esophageal wall and the arch of the aorta, posteromedially by the vertebra, anteromedially by the trachea, and antero-inferiorly by the left main bronchus. Anteroposterior and lateral roentgenograms are reproduced.

**Diagnosis and Treatment of Cardiospasm.** Porter P. Vinson. South. M. J. **40:** 387–391, May 1947.

Vinson discusses the various aspects of the entity called cardiospasm. Although the exact etiology is obscure, the condition is probably the result of a disturbance in the nerve-muscle mechanism of the esophagus with degenerative changes occurring in the vagus nerve endings and a resultant overactivity of the sympathetic system. There is, however, some disagreement about the nerve-ending degeneration theory.

Cardiospasm occurs more frequently in men than in women, in a ratio of 3 to 2. The chief symptoms are dysphagia, weight loss, regurgitation of material from the esophagus, dyspnea and cough, and epigastric pain. Physical examination gives little diagnostic aid. Radiologic studies are important, especially in demonstrating lesions from which cardiospasm must be differentiated. Among these are esophageal hiatus hernias of the short esophagus type, paraesophageal hernia, carcinoma, and diffuse spasm of the esophagus. A dilated esophagus filled with food may cast a shadow suggesting a mediastinal tumor.

There are three varieties of therapy for cardiospasm: (1) medical, (2) operative, and (3) mechanical dilatation of the cardia. In the author's experience stretching the cardia by means of large esophageal sounds or hydrostatic dilators passed over previously swallowed silk threads provides the most effective method of treatment. This procedure, he believes, will provide relief from symptoms in 75 per cent of patients treated. Plastic operations are seldom required and operations on the sympathetic nerve supply have produced no satisfactory results. WILLIS MANGES, M.D.

**Roentgen Diagnosis of Phlegmonous Gastritis.** K. Lindblom. Acta radiol. **28:** 33–36, Feb. 28, 1947.

Phlegmonous gastritis is a suppurative lesion, chiefly involving the submucosa; it is most frequently diffuse, like an erysipelas, but is occasionally localized, as a carbuncle. Some 400 cases have been recorded, almost all diagnosed at necropsy. Roentgen studies have been recorded in 9 cases reported by various authors. Only 5 of these were acute or subacute, and only 2 of them diffuse. In spite of the inhomogeneity of the material, the characteristic roentgen change seems to be "a smoothed surface of a narrow lumen with or without remnants of thick mucosal folds." This obliteration of the mucosal folds and the narrowing of the lumen correspond closely to the anatomical features of the lesion. The enormous edema and the cellular infiltrations are particularly marked in the submucosa, which may have a thickness of 1 to 2 cm.

In the case reported by the author, the phlegmon followed resection of a chronic gastric ulcer. Symptoms of an inflammatory condition in the left hypochondrium occurred. Roentgen examination revealed obliteration of mucosal folds, previously normal, and signs of thickening of the gastric wall. After chemotherapy, the mucosal pattern again returned to normal, and the thickness of the wall decreased. No other location of an inflammatory process than in the gastric wall itself would explain roentgen findings of this type, and in instances of a septic condition in the left hypochondrium these findings may be considered pathognomonic of a gastric phlegmon.

**Diverticula of the Duodenum.** A. G. Barsh. Texas State J. Med. **43:** 21–23, May 1947.

The diagnosis of duodenal diverticula is entirely radiological. The author found 32 cases in 2,100 consecutive roentgen examinations. Of the 32 cases, 22 involved the second or descending portion of the duodenum, 8 the third portion, and 2 the fourth portion. In only one instance was the diverticulum on the lateral or convex aspect of the duodenum. The etiology is not known, though weakness of the wall at the site of passage of vessels through it is thought to be a predisposing factor and increasing age a contributing factor. The author does not believe that diverticula are congenital in the sense that they exist at birth, as they are rare in young people.

The diagnosis depends on the demonstration of a mass of barium in a pouch, which is generally rounded and is attached to the gut by a pedicle of varying size and in communication with the main stream of barium. The pouch of the diverticulum may not fill at the first examination and repeated examinations may be required. Retained barium in the ampulla of Vater should not be confused with a true diverticulum.

Tenderness to pressure directly over the duodenum is an important point in determining otherwise undisclosed causes for symptoms. Evidence of inflammatory tissue in the wall of the diverticulum is rare, but the presence of heterotopic pancreatic tissue is frequent. These diverticula may give rise to symptoms as the result of ulceration. Associated gallbladder disease is relatively frequent. The diverticula about the ampulla may disturb bile drainage. In a similar way pancreatitis may be produced.

Surgical intervention is not required in most cases unless it can be shown quite conclusively that the diverticula are a direct or indirect cause of symptoms. Medical treatment is usually similar to that for peptic ulcer, plus postural drainage when bowel content is retained abnormally in the pouches.

B. S. KALAYJIAN, M.D.

**Roentgenological Contribution to the Diagnosis of Functional Intestinal Disorders.** Harry M. Weber. J. A. M. A. **134:** 226–229, May 17, 1947.

The author briefly discusses the physiology of intestinal functions in the first part of the article. After pointing out the interdependence of the various functions, he correlates clinical symptomatology with roentgenoscopic findings. A discussion follows of intestinal dysfunction associated with organic disease in the intestine itself as compared with dysfunction due to extra-intestinal disease. Finally the problem of intestinal dysfunction without demonstrable cause or association is attacked. The psychologic, as well as unphysiologic, aspects of roentgenoscopic examination are pointed out, with their effects on the interpretation of the examination. It is proposed that the roentgenologic examination that is undertaken specifically for the study of intestinal function be better adapted to that purpose, chiefly by elimination, so far as possible, of all extraneous factors that may influence intestinal function adversely. In closing, the point is made that the greatest contribution which the roentgenologic examination of the intestine makes to the diagnosis of functional intestinal disorders is the facility and accuracy with which it can be made to exclude organic intestinal disease as the cause of the clinical manifestations of dysfunction.

D. A. KOCH, M.D.
(University of Michigan)

**Benign and Malignant Tumors of the Small Intestine.** Thomas W. Botsford and Roy E. Seibel. New England J. Med. **236:** 683–694, May 8, 1947.

Tumors of the small bowel are admittedly unusual, but this in no way excuses one from considering their possibility. This study is based on a total of 65 cases of primary tumors of the duodenum, jejunum, and ileum, of which 33 were malignant.

Carcinoma of the small bowel is usually adenocarcinoma. All of the authors' carcinomas (18) were of that type. In the duodenum the tumor may arise from an ulcer or a polyp. The typical adenocarcinoma of the small bowel gives an annular constriction and is not a large tumor.

Lymphosarcoma originates in the lymphoid tissue of the bowel wall, chiefly in the ileum, with early involvement of the mesenteric lymph nodes. The lesion is usually diffusely infiltrating and a mass is often palpable.

Argentaffinoma is usually benign, and radical resection is indicated even in the presence of metastases. The tumor has a distinctive yellowish color.

Lipomas are usually located in the submucosa and may become pedunculated.

Adenomas of the small intestine are pedunculated and may undergo malignant change.

Leiomyoma is, as a rule, a small sessile tumor and rarely undergoes malignant change.

There is no characteristic symptomatology of tumors of the small bowel. However, obstruction with intussusception is not an unusual finding and bleeding may result in a secondary anemia. An important feature is the history of repeated negative x-ray examinations of the colon and upper gastro-intestinal tract, which should lead one to suspect a small bowel lesion.

In x-ray study of the small bowel a flat film of the abdomen may reveal an area of obstruction with intussusception. Direct examination may be made by serial films of the abdomen, taken at half-hour or hourly intervals, after barium by mouth. Another method is to pass a Miller-Abbott tube into the duodenum and, under fluoroscopic observation, note the progress of barium through the small bowel. Spot films, of course, are of great advantage. Still another method is to pass the Miller-Abbott tube as far as the obstructing lesion and then introduce a small amount of barium at this level to define the lesion.

JOHN B. MCANENY, M.D.

**Cholangiography Performed with the Help of Peritoneoscopy.** H. Royer and A. V. Solari. Gastroenterology **8:** 586–591, May 1947.

Using a small (4 mm.) peritoneoscope as a guide, the authors have successfully injected the gallbladder directly with a special double needle inserted through the abdominal wall. The peritoneoscope is inserted just below the liver margin and about 3 to 5 cm. lateral to the mid-line. The gallbladder is localized, and the double tube type of needle is pushed through the abdominal wall 1 cm. from the peritoneoscope. Then under direct vision the inner needle is inserted into the gallbladder. Specimens of bile may be aspirated if desired. Twenty to 40 c.c. of a radiopaque aqueous medium are injected, the instrument is removed, and roentgenograms are made immediately.

It is usually possible to visualize the gallbladder, the cystic duct, the hepatic ducts, and the common bile duct. Anatomically, the only new finding was a sharpening or beveling of one side of the terminal end of the common duct not seen previously. Physiologically, the gallbladder tends to contract uniformly without significant change in shape and no evidence of peristalsis was seen at any time. In most cases there was a contraction of the neck near the cystic duct. In some cases the dye was seen to go up into the hepatic ducts when the gallbladder contracted, suggesting failure of the sphincter of Oddi to relax. The authors could demonstrate no evidence of sphincteric action at the lower end of the main hepatic duct or of peristalsis along the common duct. Gallstones within the gallbladder were easily demonstrated, and in some cases stones in the common duct were seen. A diverticulum of the cystic duct was demonstrated in one case and in several a narrowing or obstruction at the lower end of the cystic duct was visualized.

The technic was not employed in any case in which there was evidence of acute inflammatory change in the region of the liver. No accidents or serious sequelae occurred. In some cases there was bile leakage through the puncture wound in the gallbladder, but in no instance did peritonitis develop.

B. S. KALAYJIAN, M.D.

**Report of a Case of Spontaneous Cholecystoduodenostomy.** Gordon J. Culver and John Richard Kline. Am. J. Digest. Dis. **14:** 162–163, May 1947.

A case of spontaneous cholecystoduodenostomy is presented by the authors, who succeeded in filling the gallbladder, common duct, and left and right hepatic ducts with barium. An excellent reproduction of the film showing the filled ducts accompanies this article. The history obtained from the patient, a white female aged 68, suggests that the rupture occurred about three years before it was found by gastro-intestinal examination.

JOSEPH T. DANZER, M.D.

**Roentgen Findings in Acute Pancreatitis.** John C. Glenn, Jr., and George J. Baylin. Am. J. Roentgenol. **57:** 604–615, May 1947.

A review is given of the anatomy of the pancreas, and the incidence, etiology, signs and symptoms, laboratory findings and pathology of pancreatitis. The authors state that their cases have usually shown rather persistent spasm of the duodenal loop associated in some instances with contour changes. The jejunum frequently showed marked persistent spasm of some segments along with apparent or real dilatation of others, and associated with this there was a pronounced coarsening of the folds. Also seen were constant areas of spasm in the colon at the mid-transverse portion and the splenic flexure, both regions being zones of direct contact with the pancreas.

If there is appreciable enlargement of the head of the pancreas, the duodenal loop may be widened and the valvulae conniventes flattened and the inverted "3" sign of Frostberg may be present. Some of the small intestine in the region may show alternate areas of spasm and dilatation. The duodenal bulb may be lifted or distorted. The stomach may be pushed up or forward.

An extremely important relationship of the pancreas is that with the diaphragm, for many cases of pancreatitis will show evidence of fluid at the left base due to inflammatory changes occurring in the diaphragm or beneath it. There may also be obliteration of the left psoas or renal shadows. A duodenal diverticulum which is buried within the pancreas, when inflamed, may lead to pancreatic disease. It should also be remembered that the tail of the pancreas is in contact with the diaphragm, splenic flexure of the colon, and the spleen, and inflammation in this portion of the pancreas may affect these organs. CLARENCE E. WEAVER, M.D.

## THE MUSCULOSKELETAL SYSTEM

**Polyostotic Fibrous Dysplasia: A Defense of the Entity.** Fuller Albright. J. Clin. Endocrinol. **7:** 307–324, May 1947.

This paper concerns the syndrome (Albright's) which in its complete form is characterized by (1) a disseminated osteitis fibrosa (both hyper- and hypo-ostotic) with a segmental distribution, (2) areas of cutaneous pigmentation which have a distribution suggesting some connection with the bone lesions and (3), in the female, sexual and somatic precocity.

The author believes the syndrome is not a form of lipoid granulomatosis (xanthomatosis) because: (*a*) the blood cholesterol level is not abnormal; (*b*) bone biopsies show "foam cells" only infrequently; (*c*) the bone lesions show only a slight tendency to progress, clear up spontaneously, and are not radiosensitive; (*d*) the segmental distribution of the bone and skin lesions is not suggestive of a metabolic disorder; (*e*) the x-rays show increased bone formation as well as bone destruction; (*f*) the areas of cutaneous pigmentation are not characteristic of lipoid granulomatosis; (*g*) when the disease is widespread, the serum phosphate level is high; (*h*) sexual precocity in females is not a feature of lipoid granulomatosis.

The author also believes that this syndrome is not a form of neurofibromatosis (von Recklinghausen) because: (*a*) no case has been seen or found in the literature where multiple cutaneous fibromata, a common and pathognomonic feature of neurofibromatosis, and widespread bone disease with evidence of increased as well as decreased bone formation, a common and pathognomonic feature of the syndrome, were present in the same individual; (*b*) the syndrome does not tend to run in families; (*c*) sexual precocity in females is not characteristic of neurofibromatosis, although sexual precocity, especially in males, occasionally occurs because of a neurofibroma in the region of the hypothalamus (pineal syndrome); (*d*) an autopsy on a patient with the syndrome revealed as a possible cause of the precocity not a tumor but a lesion in one mammillary body; (*e*) the bone lesions in neurofibromatosis are not extensive, do not show new bone formation, and are confined to certain localities, notably the upper ends of the tibias and the lower ends of the femurs; (*f*) the areas of cutaneous pigmentation in neurofibromatosis usually have smooth edges rather than the irregular edges which characterize the areas in the syndrome under discussion; (*g*) elephantiasis, so common in neurofibromatosis, has not been found in this syndrome.

The terminology is discussed, with the conclusion that the condition had best be termed "polyostotic fibrous dysplasia" as suggested by Lichtenstein (Arch. Surg. **36:** 874, 1938).

**Osteomalacia and Late Rickets. The Various Etiologies Met in the United States with Emphasis on That Resulting from a Specific Form of Renal Acidosis, the Therapeutic Indications for Each Etiological Sub-Group, and the Relationship Between Osteomalacia and Milkman's Syndrome.** Fuller Albright, Charles H. Burnett, William Parson, Edward C. Reifenstein, Jr., and Albert Roos. Medicine **25:** 399–479, December 1946.

This is an exceedingly comprehensive article covering in detail the points mentioned in the title. It is quite impossible to prepare an adequate abstract of it. The authors recognize four degrees of osteomalacia with respect to their severity: (1) chemical osteomalacia with normal phosphatase, (2) chemical osteomalacia with high phosphatase, (3) Milkman's syndrome, and (4) advanced osteomalacia. They regard Milkman's syndrome, characterized by multiple spontaneous idiopathic symmetrical fractures, as a form of osteomalacia for the following reasons: (*a*) there is evidence that the lesions described by Milkman are united but uncalcified fractures, and such fractures are a characteristic of osteomalacia ( *Umbauzonen* of Looser) and of no other condition; (*b*) the serum calcium, phosphorus, and phosphatase findings in classical and undoubted cases of Milkman's syndrome are those of osteomalacia; (*c*) Milkman's syndrome responds to anti-osteomalacic therapy; (*d*) the histopathology in Milkman's syndrome is that of osteomalacia.

**Osseous Congenital Syphilis: Effects of Penicillin on Rate of Healing.** Allan J. Hill, Jr., Ralph V. Platou, and John T. Kometani. J. Pediat. **30:** 547–563, May 1947.

The authors, following McLean's classification, have divided the findings in congenital syphilis of bone into three categories: osteochondritis, osteomyelitis, and periostitis. Each category has been divided into several types and a degree of severity has been arbitrarily assigned to each type. Acknowledging that their control series is imperfect, the authors have indicated the nature of the changes seen in untreated congenital

syphilis from birth to the age of twenty-four months. In general, untreated congenital syphilis tends to grow worse up to the age of three months and then subsides in severity. Late complete healing may result when early lesions are severe. Osteochondritis and osteomyelitis increase in severity up to the age of ninety days and then decrease in severity. Periostitis, however, rises more slowly to its peak at six months and then subsides.

Healing was found to be more rapid in infants treated by penicillin during the first three months of life. In those treated later, healing was slow. Analysis of the data showed no significant differences in rates of healing for treated and untreated groups unless therapy was given before the age of three months.

It is of interest that there was an increase in severity of bone lesions in some children treated within the age of three months. There is also a lag in improvement after therapy given at this age. Pseudoparalysis disappears without any specific changes in the roentgenograms. In some cases, osseous lesions may appear worse after the pseudoparalysis subsides. PAUL W. ROMAN, M.D.

**Disseminated Granuloma Inguinale of Bones.** William J. Rhinehart and John T. Bauer. Am. J. Roentgenol. **57:** 562–567, May 1947.

A review of the literature dealing with bone involvement by granuloma inguinale is given, and a case is reported. A Negro woman, aged thirty-three, had an ulcerating lesion of the cervix and a mass in the left posterior pelvis which pressed upon the rectum, sigmoid colon, and bladder. Biopsy of the vaginal lesion confirmed the diagnosis of granuloma inguinale. Roentgenographic examination disclosed the presence of osseous lesions in both tibiae, both fibulae, both ulnae, the left radius, the proximal phalanx of the right ring finger, both frontal bones, and the left astragalus. The defects in the bones were multiple, irregular, osteolytic lesions of the cortex with no evidence of sequestrum or surrounding osteoplasia. The margins of the lesions were not clear cut. There was no periosteal proliferation or periostitis. Aspiration of the tibial lesion revealed characteristic cells of granuloma inguinale containing Donovan bodies. The patient died of hemorrhage from erosion of the left hypogastric vein.

There is nothing specific in the roentgenological findings leading to a diagnosis of granuloma inguinale. The lesions are essentially osteolytic with no reaction in the overlying periosteum, and no regeneration of bone. The final diagnosis rests upon biopsy and the finding of the pathognomonic Donovan bodies and typical phagocytic cells in the microscopic preparations, and a knowledge of the location of the primary lesion.

CLARENCE E. WEAVER, M.D.

**Dislocation of the Acromioclavicular Articulation. A Note on Technique of Radiographic Examination of the Shoulder in Suspected Dislocation at the Acromioclavicular or Humeroscapular Articulation.** Charles J. Sutro. Surgery **21:** 751–754, May 1947.

Radiographic examination of the shoulder in patients suspected of having acromioclavicular separation or humeroscapular separation is routinely made in the dorsal recumbent position. Thus, the weight of the arm is removed from the shoulder, and separation of these articulations may not be recognized. The author describes a method of examination in the upright position. Anteroposterior radiographs are made at intervals during a three-minute period, while a 5- to 10-pound weight is held in the hand of the affected extremity. This gravity traction demonstrates subluxations of the head of the humerus, and luxations of the acromioclavicular articulation.

A modification of the airplane splint, having a crossed web over the acromial end of the clavicle, is used in maintaining reduction of acromioclavicular separations. Excellent illustrations and diagrams are included.

[Radiographs of clinically normal shoulders under similar traction are not included, and the possibility that some subluxation of the head of the humerus may occur with traction in normal individuals is not considered.—J. E. W.] J. E. WHITELEATHER, M.D.

**Monteggia Fracture.** G. J. Curry. Am. J. Surg. **73:** 613–617, May 1947.

A Monteggia fracture is a fracture of the upper end of the ulna with radial head dislocation. It may be produced by indirect or direct violence, the basic reason being that the radius and ulna form mutual splints, each bound to the other at the top and bottom by strong ligaments and attached almost throughout by the strong interosseous membrane. The ulna fractures and shortens, thereby putting stress and strain on the radial head, which becomes dislocated. A dislocated radial head should, therefore, be suspected when there is a fracture of the ulnar shaft 4 or 5 inches from the elbow. Neglect of this condition may result in a severe disability. Two types of displacement are described: (1) the flexion type, occurring in 10 to 15 per cent of the cases, in which the radial head is dislocated backwards with the ulnar fracture angulation in the same direction; (2) the extension type, presenting anterior angulation of the ulnar fracture and a radial head displacement upwards and outwards.

A case is presented in which the radial head dislocation was severe and the destroyed orbicular ligament was replaced by a segment of the pronator fascia of selected length and width. This followed internal fixation of the ulnar fragments. A satisfactory result was obtained. Roentgenograms are reproduced.

**Pneumoradiography of the Knee Joint.** O. Häuptli. Schweiz. med. Wchnschr. **77:** 549–551, May 24, 1947.

The author employs carbon dioxide as a contrast medium in roentgen study of the knee joint and recommends an injection pressure of 100–150 mm. of water. In most instances the use of an iodine preparation for double contrast is contraindicated because of the frequent complications. Perfect asepsis is essential. The anteroposterior film is made in semiflexion with the central ray parallel to the tibial joint surface; the other view is taken in latero-medial projection. Close supervision by the roentgenologist and co-operation with the surgical staff are essential to obtain sharp pictures. The escape of gas into the periarticular structures indicates the presence of a tear, which may have been produced by earlier trauma or may be due to the injection as a result of an abnormally weak capsule or excessive injection pressure. In the author's hospital, at Aarau, the examination is often done on an outpatient basis, the only restriction being prohibition of active sports and marching for the following two days. No case of infection resulted from this procedure in 1,622 patients studied from 1935 to 1947.

The reliability of the interpretations has been determined by operative check. Meniscus tears with dislocation of the fragment can be readily identified. Tears without displacement of the fragment cannot be seen. Asymptomatic lesions demonstrated by x-ray have been repeatedly verified at operation. Negative findings are often important in determining the prognosis. Cases with obscure clinical findings are especially worth study by this method, as the diagnosis can be clarified in 90 per cent of these.

The normal meniscus fuses into the joint capsule with a smooth, regular curve. There is great variation in the size of the meniscus. If the entire meniscus is slightly separated from the tibia and shifted toward the capsule, it is termed "*laxité*" (relaxation) after the French school; greater separation, especially with narrowing of the joint cartilage, is characteristic of a traumatic lesion. The edges are then sharply demarcated. Many forms of the meniscus are seen; meniscus bipartitus, menisci of varied height and length, etc. In the presence of tears, the meniscus may take on bizarre forms. The formation of a step, most commonly on the tibial spine, is especially characteristic. Oblique views are often very informative.

The shadow of the lateral meniscus is ribbon-like, and generally overlies the lateral femoral condyle. It appears raised from its inferior attachment, a normal finding. Changes in the lateral meniscus are hard to demonstrate; they are best shown in a lateral oblique view. In general, the diagnosis of disease of this structure is more difficult and less reliable than corresponding diagnoses for the medial meniscus. Even more difficult is the study of the cruciate ligaments; they may only occasionally be seen near the cortex of the intercondylar fossa. Osteochondritis is often easily diagnosed, as the cartilage defect is directly visualized. Loose bodies show well, and Hoffa's fat pad is clearly demonstrable. LEWIS G. JACOBS, M.D.

**Complications of Myelography by Abrodil.** K. Lindblom. Acta radiol. **28:** 69–73, Feb. 28, 1947.

In 721 patients on whom myelography with abrodil was carried out, complications (headache, stiff neck, shock, lumbar pains, hyperesthesia) were reported more than 54 times. The myelographies were performed by two different technics, that described by Arnell (Acta radiol. **25:** 408, 1944. Abst. in Radiology **46:** 303, 1946) and Lindblom's modified form (Acta radiol. **27:** 1, 1946. Abst. in Radiology **48:** 101, 1947).

For avoiding complications in abrodil myelography the following suggestions are made: A fine needle should be used for the puncture (0.5 mm. with an introducer for the puncture of the skin and the ligaments). The patient should be prepared against drop in blood pressure; ephedrine should be given when the pressure drops. The head should be raised only during the examination. The anesthetic solution should not be too heavy; 1–2 c.c. of a 5 per cent solution of novocaine is recommended. Only approved radiopaque solutions, as 20 per cent abrodil, should be used.

**Early Localization with the Use of Pantopaque of an Acute Epidural Spinal Abscess.** Abraham Kaplan and Arthur Lautkin. New York State J. Med. **47:** 1021–1023, May 1, 1947.

Acute epidural spinal abscess is a surgical emergency which can be recognized before the onset of neurologic signs. A history of antecedent local infection, such as a furuncle, paronychia, acute sore throat, or osteomyelitis, followed several days or weeks later by an acute onset of fever, chills, and excruciating localized back pain, is very suggestive of this diagnosis. There is usually evidence of acute illness, some stiffness of the neck, and extreme localized spinal tenderness. Spinal fluid studies will show complete subarachnoid block, xanthochromatic fluid, and increased total protein. Myelography with 5 c.c. of pantopaque should follow immediately. The level at which the medium is arrested will accurately establish the site of the lesion. Immediate laminectomy, with removal and/or drainage of the infected material will save lives immediately and also prevent the tragic complications of paralysis of the bladder and rectal dysfunction, decubitus, ascending urinary infection, and a drawn out death from renal failure.

The authors report what they believe to be the first case of epidural abscess in which the diagnosis was confirmed by myelograms with pantopaque and laminectomy was immediately done with excellent results.

B. S. KALAYJIAN, M.D.

**Congenital Dermal (Pilonidal) Sinus with Dural Connection. Case Report and Discussion.** Eugene E. Cliffton and John R. Rydell. J. Neurosurg. **4:** 276–282, May 1947.

A case of congenital sacral dermal sinus in communication with the dural sac and in direct continuity with the filum terminale is presented. X-rays of the spine revealed spina bifida occulta of the entire sacrum. The findings on myelography are of particular interest. Fluoroscopy and films showed the pantopaque, as it flowed caudally, to split into two columns. The linear defect formed in the pantopaque column began to the right of the mid-line near the lower edge of the 5th lumbar vertebra and extended downward and medially to the mid-line over the 1st sacral segment. The findings are considered evidence that dermal sinuses in this area originate as malformations in development of the neural canal.

## GYNECOLOGY AND OBSTETRICS

**Radiography of the Lymphatic System of the Uterus.** Charles Várady. Schweiz. med. Wchnschr. **77:** 509–510, May 3, 1947.

Although reflux of contrast medium into the uterine veins is a not too rare complication of hysterosalpingography, reflux into the lymphatic system has not been previously observed. Such an accident is reported in a 40-year old woman, who was being studied for sterility. After injection of Iodipin both tubes were found to be obstructed. Oil was also scattered through the uterine wall in a streaky fashion, filling the lymphatics. It reached the iliac nodes, so as to render them opaque, in about fifty minutes. The patient suffered no ill effect from the accident. The author proposes the term "uterolymphatic influx" for this condition, and feels that so rare and harmless an accident does not contraindicate so useful a procedure as hysterosalpingography. LEWIS G. JACOBS, M.D.

**Standardised Radiological Pelvimetry. IV. Interpretation of Pelvimetry.** E. Peter Allen. Brit. J. Radiol. **20:** 205–218, May 1947.

While it is true that roentgen pelvimetry supplies in-

formation only about the bony factors in delivery and that these constitute but one phase of the problem, the author believes that on the basis of pelvic measurements alone a reasonably accurate prognosis of the probable course of labor can be offered in the majority of cases.

After a careful correlation of a large number of cases, he has worked out a relatively simple prediction table, assuming the fetal head to have a diameter of 100 mm. For larger heads corrections must be made.

Vaginal delivery is certain without evidence of disproportion when the conjugate is over 130 mm.; the brim area is over 130 sq. cm.; the mid-plane area is over 120 sq. cm.; the bispinous diameter is over 110 mm., and the posterior sagittal of the outlet is over 65 mm.

Vaginal delivery is reasonably certain, but forceps may be required, when the conjugate is between 105 and 130 mm.; the brim area is between 105 and 130 sq. cm.; the mid-plane area is between 95 and 120 sq. cm.; the bispinous is between 90 and 110 mm., and the posterior sagittal of the outlet is between 50 and 65 mm.

Vaginal delivery is uncertain and if possible will show clear evidence of disproportion when the conjugate is between 90 and 105 mm.; the brim area is between 85 and 105 sq. cm.; the mid-plane area is between 80 and 95 sq. cm.; the bispinous is between 80 and 90 mm., and the posterior-sagittal of the outlet is between 45 and 50 mm.

Vaginal delivery is unlikely and section is justified in measurements below the lower limits given above.

[Abstracts of the earlier papers in this series appear in Radiology **50:** 137 and 272, January and February 1948.] SYDNEY J. HAWLEY, M.D.

## THE GENITO-URINARY SYSTEM

**Genitourinary Conditions in Infants and Children.** Herman L. Kretschmer. J. Pediat. **30:** 603–636, May 1947.

In this long treatise all of the usual lesions of the genito-urinary tract are described. The interesting feature lies in the fact that the cases were diagnosed before the patients reached the adult stage of life. The author briefly describes and considers each of the well known congenital anomalies. Some of these are illustrated by case reports.

A comprehensive description of obstructive lesions of the vesical neck places these lesions in two categories: (1) those causing mechanical obstruction; (2) those on a neurologic basis.

Two types of renal tuberculosis have been observed: (1) renal involvement as a part of general miliary tuberculosis and (2) surgical renal tuberculosis. The author believes that with the increased use of diagnostic urologic methods in children more cases of chronic renal tuberculosis are being recognized. He does not believe that renal tuberculosis in children is rare but that it has often been overlooked. The article contains no photographs or roentgenograms of these cases.

The problem of urinary calculi in children is reviewed. The findings are the same as in adults. Hydronephrosis and hydroureter are due to the usual cause, obstruction either from within or from outside the tract.

The most common malignant tumor of the genitourinary tract in children is the Wilms' tumor. Preoperative deep roentgen therapy, followed by nephrectomy when the tumor no longer diminishes in size, and then by a further course of irradiation, has brought about a great reduction in the operative mortality.

"The common bladder tumor of infancy and children is the sarcoma." STANLEY H. MACHT, M.D.

**Complete Urologic Examination in Infants and Children with Urinary Infection: Indications and Importance.** Meredith F. Campbell. M. Clin. North America **31:** 659–667, May 1947.

Attention is directed to the high incidence and potential gravity of urinary infections in the young. At the present time more urologic examinations are done in infants and children for pyuria than for any other reason. Careful urinalysis of properly collected specimens should be carried out before subjecting any patient to instrumental investigation because of urinary infection; the invading bacteria should be precisely identified and an attempt made to sterilize the urine by medical treatment.

Excretory or intravenous urography may be expected to give a satisfactory roentgen delineation of the upper urinary tract in at least 50 per cent of children in whom it is employed. Such a study will often direct special attention to one kidney and/or ureter at the time of cystoscopy and retrograde pyelography. In general, the younger the patient the less likely is the excretory study to be of diagnostic value.

Since modern chemotherapy may be successful in eradicating a chronic urinary infection even in the presence of obstruction, calculi, and other major urologic lesions, an excretory urographic study, at least, should be made before the patient is discharged as cured, to determine that the upper urinary tract is morphologically normal. Excretory urograms may, however, be misinterpreted and surgical attack on the upper urinary tract and particularly nephrectomy should not be carried out on that basis alone except in those rare instances in which ureteral catheterization cannot be performed, as in tuberculous obliterative ureteritis, ureteral hypoplasia, or because of insurmountable technical difficulty.

**Agenesis of the Right Kidney with a Retroperitoneal Cyst Arising in a Persistent Metanephros.** M. F. Weingarten, John M. Orem, and O. C. Cox. J. Urol. **57:** 829–833, May 1947.

According to the authors, this is only the third case to appear in the literature of agenesis of a kidney with the concomitant finding of a retroperitoneal cyst. The first was reported by Krauss and Straus (J. Urol. **34:** 97, 1935), and the second by Kornblum and Ritter (Radiology **32:** 416, 1939).

The authors' patient was an adult male who was operated upon for appendiceal abscess. No abscess was found, but a long, clubbed, red appendix was removed. At the same time there was discovered just above the bladder a large extraperitoneal cystic mass. To avoid peritoneal soiling, removal of this mass was postponed to a later date. In the meantime cystoscopy, retrograde pyelography, and intravenous pyelography showed absence of the right renal shadow and no right ureteral opening in the bladder, displacement of the bladder downward and to the left by a pelvic mass, and hypertrophy of the left kidney.

The cystic mass was subsequently removed by extraperitoneal approach. Its fluid content was approximately 500 c.c. Tissue study showed a columnar epithelial lining with inner circular and outer longitudinal muscle fibers. Fibrous tissue was abundant and

replaced muscle tissue in certain areas. The picture was that of a congenital metanephric cyst, without evidence of malignancy.

The authors believe that the findings in their case are to be explained by non-union of the metanephric mass and ureteric bud to form the right kidney. As a result the metanephric mass remained in its fetal position and proceeded to normal development with the formation of a cyst as the result of accumulating secretion. Absence of the kidney on the right led to a compensatory hypertropy on the left. JOSEPH P. TOMSULA, M.D.

**Significance of Retrograde Pyelography in the Diagnosis of Paranephritic Abscess.** Hubert Mäder. Schweiz. med. Wchnschr. **77:** 560–564, May 24, 1947.

The clinical and laboratory findings in paranephritic abscess are often such as to leave the diagnosis doubtful. Plain films of the abdomen, if there is good clearing of the gas shadows, may show a diffuse haziness of one kidney region, irregular broadening of one kidney shadow with poor definition, disappearance of one psoas shadow, elevation or immobility of the diaphragm on the affected side, a secondary pleurisy, or scoliosis toward the affected side, but since these signs occur in other surgical conditions they do not of themselves lead to a diagnosis. Urographic study gives additional information. With the intravenous method, the kidney shadow on the diseased side is denser and larger; the ureter is shown clearly throughout its length, and the kidney is displaced by the mass of the abscess. Retrograde pyelography shows displacement of the kidney, rotation and imbalance of the entire pelvic system on all axes, compression of the pelvis, filling defects, and deformity of the calices. All of these findings arise from external pressure. Study of the respiratory excursion of the kidney is of no conclusive significance. Tumors may give rise to a similar picture, but the general clinical findings will distinguish these. A lateral pyelogram is of great value; in 90 per cent of cases there is forward displacement of the kidney, so that it lies in front of the vertebral bodies.

LEWIS G. JACOBS, M.D.

**Translumbar Aortography, an Aid in the Management of the Hydronephrotic Kidney.** A. Keller Doss. South. M. J. **40:** 376–381, May 1947.

A discussion is presented of translumbar aortography in the study of renal surgical problems. Anatomically the value of the information obtained by outlining the renal arterial tree is obvious, particularly in the diagnosis of embryologic abnormalities. From the point of view of physiology and pathology, the usefulness of the procedure, though less striking, is becoming more apparent as clinical and pathological studies demonstrate the association of certain abnormalities of the renal arterial pattern with various syndromes and specific entities.

The author has devoted himself chiefly to the use of aortography as an aid in the management of hydronephrosis. It is his practice to obtain an arteriogram before undertaking renal exploration, and the knowledge thus obtained has often proved the deciding factor in answering the question: Should an effort to save the kidney be made or should it be removed? Accepting the policy that a kidney is no better than its arterial supply, he makes every effort to preserve hydronephrotic kidneys in which this is adequate, reserving nephrectomy for those in which the circulation is poor. It is his belief that surgeons should be more conservative in the treatment of hydronephrotic kidneys, especially in the young.

Eight cases are briefly presented, with reproductions of arteriograms and retrograde pyelograms. In a number of instances the two were obtained in combination. The renal arterial circulation is clearly demonstrated.

WILLIS MANGES, M.D.

**Roentgenological Localization of Ureteral Obstruction by Non Radio-Opaque or Indistinguishable Calculi.** G. Gill and W. Light. Canad. M. A. J. **56:** 513–519, May 1947.

The authors describe a method of localizing exactly the offending agent causing ureteral obstruction, be it opaque or non-opaque. Intravenous urography is used to demonstrate the site of obstruction. Following the administration of 20 c.c. of dye, films are taken at five-minute intervals for the first fifteen minutes (abdominal compression must not be used, since the method is essentially functional). These afford the authors' first roentgen sign, namely *early radiologic evidence of ureteral block*. The first few films show a clear-cut outline of the collecting system on one side and lack of visualization of the collecting system on the other side; *i.e.*, one kidney excretes the dye promptly and the other not at all.

On subsequent films, obtained at intervals of fifteen minutes, the shadow of the kidney on the involved side, which was not at first clearly distinguishable, becomes visible, appearing denser and denser with time, until it stands out more prominently than the normal kidney on the opposite side. This *impregnation of the renal parenchyma* constitutes the second radiological sign.

Now that the parenchyma is densely impregnated with dye, the minor and major calices begin to show up, and in subsequent films, made at intervals of fifteen or thirty minutes, the renal pelvis is seen filled with dye, and the ureter is demonstrable. The dye comes slowly down the ureter until it is sharply halted, indicating beyond question the site of obstruction. This third sign is called by the authors *the stasis*.

By the time the obstruction is localized, it is noted that the dye outlining the collecting system on the normal side has come and gone. The radiograph now obtained is a mirror image of the visualization of the collecting system at the beginning of the examination. This confirmatory sign has been called a *reverse visualization of the collecting system*.

In 51 cases in which this procedure was used, it led to the localization not only of 25 easily distinguishable stones, but also of 20 which were otherwise indistinguishable from a maze of calcifications and phleboliths, and of 6 that were definitely not radiopaque. Five case histories are included, and films are reproduced. DANIEL WILNER, M.D.

**Pseudo-Sphincter Formation in Neurogenic Bladder.** Charles Ney, Oscar Auerbach, and Thomas I. Hoen. J. Urol. **57:** 858–868, May 1947.

In the course of their studies on the neurogenic bladder, the authors encountered a sphincter-like structure, designated as a pseudo-sphincter, in 8 of 21 paraplegics. It was situated in the prostatic urethra, just distal to the colliculus seminalis (verumontanum) in the region of the inferior crista. It was pale to pinkish red, with a

sharp or more or less rounded corrugated edge. Microscopically it was lined by transitional-cell epithelium and composed of connective tissue with some hyalinization. An extensive acute or chronic inflammatory process with edema was present. Submucosal glands and a small amount of muscle were found.

Three cases are reported in detail. Cystourethrograms were obtained in one case, revealing division of the prostatic urethra into a proximal dilated portion and a distal portion which tapered into the membranous urethra with some narrowing in the region of the internal sphincter.

The significance of the pseudo-sphincter is not explained. The authors express the belief that it represents the boundary between the prostatic urethra, which arises embryologically from terminal portions of primary excretory ducts, and the distal prostatic urethra, which arises from the urogenital sinus.

PAUL R. NOBLE, M.D.

## SINUS TRACTS AND FISTULAS

**Roentgenographic Demonstration of Sinuses and Fistulae.** Robert C. Pendergrass and William C. Ward. Am. J. Roentgenol. **57:** 571–577, May 1947.

The use of iodized oil was found to be helpful in the investigation of complicated war wounds in an army general hospital that was treating a fairly large number of spinal cord and cauda equina injuries. With aseptic technic a small rubber catheter or rubber-tipped syringe was inserted into the external opening and the iodized oil was injected under roentgenoscopic observation. "Spot" films were often used. Stereoscopic and lateral views were also considered essential. Barium and air studies of the colon were sometimes used in combination with the sinus tract injection in instances of fecal fistula. Iodized oil was not injected in any case in which a spinal fluid fistula was suspected.

Six cases are presented in which essential information was obtained by lipiodol injection in these difficult sinus tract cases. In one case of fecal fistula through the sacrum and the fifth lumbar interspace, communication with the sigmoid colon was shown by lipiodol injection. A transverse colostomy was done and complete healing of the fistula followed. In another case a urinary fistula through a wound in the region of the fifth lumbar vertebra was found to communicate with the lower end of the left ureter. A left nephrectomy was performed. In a third case there was a communication through an abscess in the right upper abdomen into a small bile duct. Better drainage was established and the fistula healed.

CLARENCE E. WEAVER, M.D.

## RADIOTHERAPY

**Treatment of Malignant Melanoma. Report of 862 Cases.** George T. Pack, S. L. Perzik, and Isabel M. Scharnagel. California Med. **66:** 283–287, May 1947.

An analysis of 862 cases of malignant melanoma, of which 595 were available for five-year end-result study, with an over-all salvage of 9.7 per cent, is presented. Before 1935, irradiation was the primary mode of treatment: x-rays, telecurie therapy by a large radium bomb or pack, superficial radon plaques, and the interstitial deposition of gold radon seeds. Since 1935, surgery has been the primary therapeutic agent. In these two groups of unselected cases of localized melanoma, surgical treatment secured five times the salvage for three years and twenty-three times the salvage for five years that was obtained by primary irradiation. Whenever metastases to regional lymph nodes had occurred, the salvage at three years was nearly three times greater and at five years two and one-half times greater as a result of predominantly surgical treatment.

A comparison of all patients with localized melanomas treated by irradiation and by surgery, regardless of the time period, shows that surgery yielded 38.4 per cent salvage at three years, as against 1.6 per cent for irradiation; and 17.7 per cent as against none for five years. The same proportionate increase in salvage is revealed in the treatment of patients with metastases to the regional lymph nodes. Included in the analysis are 18 patients surviving from ten to seventeen years, all of whom had undergone surgical treatment, with or without irradiation. No patient was treated solely by irradiation. All these patients had dissection of the regional nodes, and in 7 the nodes showed metastases.

**Malignant Lymphoma: Value of Radical Surgery in Selected Cases.** C. Alexander Hellwig. Surg., Gynec. & Obst. **84:** 950–958, May 1947.

From January 1925 to December 1945, 234 cases of malignant lymphoma were studied in the Pathological Department of St. Francis Hospital, Wichita, Kansas. Histologic material was available from all of these cases, but only 130 with complete clinical and adequate follow-up records are used in this analysis.

The general outline of Gall and Mallory's classification (Am. J. Path. **18:** 381, 1942) is adhered to, with the substitution of Lymphatic Tumor Registry terms for some of their less familiar designations. Most of the malignant lymphomas fall into 4 groups, namely, reticulocytoma, Hodgkin's disease, lymphoblastoma, and lymphocytoma.

Compared with other types of cancer, malignant lymphoma is not common. The present series represented slightly less than 5 per cent of all cancers examined during a twenty-one year period. The average age at onset—*i.e.*, appearance of the first relevant symptom—was 44.7 years. In general, the disease is rare before twenty and after seventy years.

In this material, which included complete autopsy studies on 30 cases, an extra-nodal primary focus was found in only one-third of the patients. In 26 cases of the 130 it was reasonably assumed that the primary focus arose in one of the cranial structures, the tonsils and nasopharynx being the most common sites. The gastro-intestinal tract furnished the primary site in 19 cases. It is believed that in a majority of instances the disease begins and runs its early course in the lymph nodes alone.

Cervical nodes represented the primary site of lymph node involvement in 40 per cent of the series; axillary nodes in 9 per cent; inguinal nodes in 13 per cent; abdominal nodes in 4 per cent. Mediastinal nodes were enlarged in 8 per cent, and the disease appeared to involve almost the entire node system simultaneously in less than 2 per cent. Numerous organs were involved secondarily, including the liver, spleen, lungs, pleura, skin, and bones. The average duration of life from onset was only 26.7 months.

The fact that the malignant lymphomas are extremely radiosensitive is pointed out, but it is felt that roentgen therapy does not lengthen the survival period except in cases of large intrathoracic masses which are a rather immediate threat to life. Only 2 of 40 patients survived the five-year period following treatment by irradiation alone after the biopsy diagnosis.

The pessimistic view that surgery is contraindicated in the treatment of malignant lymphoma is presumably on the basis that the disease is essentially systemic. Ten per cent of the autopsy cases of this series showed single localized lesions accessible to surgery. Sixty-seven patients were operated upon, and of the 63 who survived the operation, 21 received no other form of therapy and 42 received external irradiation. Twelve of the 21 survived five years or longer and none showed any evidence of disease at the time of the report. In 40 cases, radical removal of a single focus was followed by adequate radiation therapy; 18 of the 40 survived, and 9 were still without clinical evidence of disease.

It is concluded that as long as malignant lymphoma is confined to an accessible single mass there is an excellent chance for obtaining a cure by complete surgical removal of the primary focus.

ALTON S. HANSEN, M.D.

**Discussion on the Treatment of Cancer of the Tongue.** Stanford Cade, Ralston Paterson, W. R. Douglas, W. L. Harnett, and Anthony Green. Proc. Roy. Soc. Med. **40:** 409–418, May 1947.

This report contains the addresses of five British radiologists and surgeons delivered before a joint meeting of the two groups. Both the radiation and the operative aspects of the therapeutic approach to cancer of the tongue are discussed.

The important factors which determine the choice of technic of treatment are the site, extent and macroscopic type of the lesion and, to a lesser extent, the histologic classification of the degree of malignancy. Enlarged cervical nodes vitally affect the prognosis but do not *per se* determine the treatment of the primary growth.

Radiation is generally accepted to be the first choice as a therapeutic measure for the primary growth. For lesions of the anterior part of the tongue, insertion of radium needles is indicated. The total dose varied in Cade's cases from 6,000 r to 9,000 r delivered in 168 hours; the dosage rate showed an equally wide range, from 30 to 75 r/hr. He used teleradium for lesions of the vallecula, epiglottis, glossopalatine folds or in the postero-lateral group spreading to the alveolar mucosa or palate. Two treatments of fifty minutes each were given five days a week. The average tissue dosage was between 5,000 and 6,000 r.

In the treatment of cervical lymph nodes, no method of irradiation can so far compare with surgical removal. The operation should consist of removal of the deep cervical fascia from the level of the mandible to the clavicle; the sternomastoid muscle, the internal jugular vein, the anterior belly of the omohyoid and often the posterior belly of the digastric are removed, together with the lymph nodes in the anterior and submaxillary triangles.

That group of infiltrating growths without palpable lymph nodes but in about 35 per cent of which these subsequently appear after the primary lesion has been controlled present a special problem.

The main theme of Paterson's contribution is the superiority of radium therapy in lingual cancer. He reported 63 per cent five-year survivals in 138 cases.

Douglas carried out a series of prophylactic block dissections and found metastatic nodes in 18 per cent. In the remainder, no metastatic tissue was found after careful pathological search. Moreover, in the 18 per cent with metastases the results were little better than if the procedure had been deferred until the nodes had appeared. A "watch technic" is now recommended: a close, intensive period of delay until nodes become palpable.

M. WENDELL DIETZ, M.D.

**Roentgen Therapy in Cancer of the Larynx.** Maurice Lenz. J. A. M. A. **134:** 117–121, May 10, 1947.

Lenz presents 110 cases of carcinoma of the larynx which have been studied in detail. The patients received roentgen therapy at the Presbyterian Hospital (New York) between 1931 and 1941. Thirty of them were free from clinical evidence of cancer between five and fourteen years after treatment.

Treatment was in accordance with the main principles laid down by Coutard in 1919. Important is an accurate estimate of the extent of the disease, familiarity with laryngoscopy for guidance as to daily dosage, and careful setting up of the field of treatment. Treatment should never be entrusted solely to a technician.

The author's present technic calls for administration of an average tumor dose of 5,700 to 7,000 r in five to six weeks. Treatments are given once daily, 100 r (in air) to each of two fields at 20 r per minute, with the following factors: 200 kv., 2 mm. copper or Thoraeus filter, target-skin distance 50 cm. A total of 3,000 to 3,500 r (in air) are given to each field. The average size of the field is 6 × 8 cm. with upper limits of 8 × 10 cm. In simple cancer of the vocal cord a field 6 × 6 may be used.

The author adequately outlines lymph drainage of the larynx and surrounding structures and emphasizes its importance in determining ease of extension of the primary tumor in prognosticating the possibilities of adequate response and curability.

It is concluded that roentgen therapy in early carcinoma of the cords gives as high a rate of cure and a better voice than does laryngofissure. Of importance is the conclusion that roentgen therapy is recommended in all cancers of the vocal cords except those in which the cancer has extended subglottically or into the arytenoid cartilage. In these latter cases laryngectomy followed by roentgen therapy is preferred if clinically or microscopically there is persisting cancer. With definite fixation of the arytenoid cartilage, roentgen therapy should not be substituted for laryngectomy unless there are valid reasons for avoiding this operation.

For carcinoma of the epiglottis, ventricular band, and anterior portion of the aryepiglottic folds, roentgen therapy should be employed even after fixation of the arytenoids and the occurrence of lymph node metastases.

Roentgen therapy, in the author's vast experience, has failed to cure carcinoma of the piriform sinus with its usual invasion of the arytenoid cartilage and early lymph node metastasis. Prognosis is grave when cancer of the cord or piriform sinus has metastasized to lymph nodes. If the nodes are movable they should be resected and, if fixed, treated by radium or x-rays. The prognosis is less grave if these metastases are second-

ary to carcinoma of the epiglottis or band. These should receive roentgen therapy.

R. W. BYRN, M.D.
(University of Michigan)

**Roentgen Therapy of Operable Carcinoma of the Vocal Cord (18 Cases Treated from 1921 to 1940).** Giovanni F. Gardini. Radiol. med. (Milan) **33:** 225–244, May 1947.

The author divides carcinomas of the vocal cords into four groups. Group I includes those cases in which the invasion is limited to the two anterior thirds of the cord; Group II those in which the anterior commissure is involved; Group III those with fixation of the cord and extension into the larynx; Group IV those with involvement extending beyond the larynx. Eighteen cases treated in the Curie Foundation and followed over a period of more than five years are reported. These cases were treated with roentgen rays alone with the following factors: 180 kv., 10 ma., 50 cm. distance, filtration 1 mm. copper. The dose was 200 r daily over a period of six weeks over two small fields with a total skin dose of 6,000 to 8,000 r. All the cases treated belonged to Groups I and II and over 88 per cent of the patients were well at the end of five years. These results compare very favorably with those obtained by surgery. CESARE GIANTURCO, M.D.

**Supervoltage Roentgen Therapy of Carcinoma of the Esophagus.** Franz Buschke and Simeon T. Cantril. J. A. M. A. **134:** 127–129, May 10, 1947.

The authors point out that the purpose of their paper is an attempt to overcome the attitude of defeatism that prevails in the medical profession at large, as well as among surgeons and even many radiotherapists, in regard to any therapy of esophageal carcinoma.

Nineteen patients with esophageal carcinoma have been seen by the authors since 1939. Only 6 were adequately treated by them, and of these 2 are living and well, one seven years after x-ray therapy and one two years after x-ray therapy. In each of these 2 cases approximately 5,000 r were given to the tumor (4,400 and 4,950), which the authors state is necessary over a period of about forty days for complete sterilization.

Million-volt radiation was used, the authors claiming that thus a sterilizing tumor dose of 5,000 r is obtained without undue effects on normal structures through only an anterior and a posterior port. With radiation in the medium-voltage range, this adequate dosage would be impossible without intolerable damage to surrounding structures and the patient's general condition. Overdosage is to be avoided. A forced increase in dose interferes with curability through intolerable side effects (pulmonary fibrosis).

The authors state that hospitalization is essential while treating these cases, that gastrostomy is a contraindication to treatment in the medium voltage range, but that this rule may occasionally be set aside in using million-volt radiation. They state further that radiation therapy will be tolerated only in patients with incomplete stenosis, in whom feeding is still possible, and whose general condition is good. Papillary growths show a more favorable response than the infiltrating types.

The authors in the main are attempting to show that theoretically, if a tumor dose of 5,000 r be considered a sterilization dose of radiation (over a period of forty days), therapy in the million-volt range should accomplish a certain number of cures in esophageal carcinoma, if the problem of sterilization is actually one of adequate tumor dose. They state that although the results they have presented to date are meager, they are in accordance with their theoretical considerations and are encouraging enough to justify further attempts with this procedure. R. W. BYRN, M.D.
(University of Michigan)

**Results of Treatment of Epidermoid Carcinoma of the Anus and Rectum.** Richard H. Sweet. Surg., Gynec. & Obst. **84:** 967–972, May 1947.

The differences between adenocarcinoma of the rectum and epidermoid carcinoma are stressed and the rarity of the latter is pointed out. At the Palmer Memorial Hospital (Boston) epidermoid carcinoma constituted only 4.7 per cent of 802 consecutive cases of rectal carcinoma.

In a series of 67 cases of which 48 were treated by radical surgery and 19 by irradiation, the surgical procedures were found to be superior from the point of view both of cure and palliation.

Charts setting forth the results of treatment include the following figures:

| | Cases |
|---|---|
| Radical operation | 48 |
| Died | 31 |
| Untraced | 2 |
| *Cured* | 12 (25%) |
| Alive and well (but less than three years) | 3 |
| Irradiation | |
| X-ray | 7 |
| Died (no local palliation) | 7 |
| Radium | 12 |
| Died (2 of intercurrent disease; local palliation in 6) | 11 |
| Cured (eleven years) | 1 |

JOHN O. LAFFERTY, M.D.

**Preliminary Report on Transvaginal X-ray Treatment of Carcinoma of the Cervix.** H. B. Elkins. J. Iowa State M. Soc. **37:** 196–198, May 1947.

The advantage of transvaginal roentgen therapy for carcinoma of the cervix is that lethal or near-lethal doses may be delivered to parametrial tissue without simultaneously applying necrotizing or destructive doses to the cervix, as is frequently the case when radium is employed. Of 322 cases of carcinoma of the cervix treated in the Radiological Department of the College of Medicine of the University of Iowa, 92 received external and transvaginal x-radiation alone, while the remainder were treated by other methods, chiefly combinations of x-ray and radium.

The cases were classified according to the Schmitz method, and comparative survival rates were obtained on a three-year basis. No cases in Group 1, and only 6 cases in Group 2 were treated by the transvaginal method. In Group 3 a higher survival rate was obtained by external radiation and radium than by external irradiation and transvaginal roentgen therapy. In group 4, however, the three-year survival rate is enhanced by transvaginal irradiation, since a higher dosage can be delivered to a wider field than with radium.

The method and complications are briefly discussed. Only one death could be attributed to irradiation, and in only two other cases were symptoms severe enough to require colostomy or ureterostomy.

LOUIS BERNSTEIN, M.D.

**Primary Carcinoma of the Fallopian Tube.** Erik Block. Acta radiol. **28:** 49–68, Feb. 28, 1947.

Of 16 cases of tubal cancer seen in the Radiumhemmet, Stockholm, 6 were definitely primary tubal cancer and the remaining 10 probably were so. Four cases were bilateral, 9 occurred on the left side, and 3 on the right. Ten of the 16 patients had had children. One had had an ectopic pregnancy and an abortion.

The diagnosis was not recognized prior to operation in any of the cases, and in 4 not until the specimens came to the pathologist. The original diagnosis in most instances was ovarian tumor, in a few chronic salpingitis, and in 1 myoma. At the time of operation the cancer was apparently confined to the tubes in 7 of the patients. However, all were more or less adherent to the adjacent organs. In 5 cases the ovary was involved; in 4 there was extension to the pelvic peritoneum, and in 1 to the uterus as well.

In the discussion of the results of treatment, 2 cases were excluded—one because the treatment was not yet completed and the other because the patient was treated outside the Radiumhemmet.

It is routine procedure at the Radiumhemmet not to remove the uterus in cases of carcinoma of the ovaries. Radium placed in the uterus comes in closer contact with the area of recurrences than that which is placed in the vagina. The procedure in radiologic treatment of tubal cancer is practically the same as in cancer of the ovary—namely, one intra-uterine or vaginal radium application followed by roentgen irradiation to two anterior and two posterior fields. The radium dose has varied, in the uterus 990–1,500 mg. hr., in the vagina 1,800–3,000 mg. hr. The roentgen dose has also varied. In later years, 3 × 400 r to each of four fields are administered in the first series, followed three months later by a second series of 2 × 400 r to each field. None of the cases in this series received preoperative treatment.

Of the 14 patients 7 were living and free from evidence of disease for 22, 10, 10, 4, 3, 2 and 1 years, respectively. One patient was in such poor general condition that treatment could not be completed, and death occurred in about four months. Nothing certain can be said about the prognosis in the last 4 patients.

From a study of these cases it is believed that an improvement of the results might be obtained by an early diagnosis, by a radical removal of involved tissues, and by a combined intra-uterine radium application and roentgen treatment.

Surgery should include the removal of the adnexa on both sides. Tubes which are removed on the preoperative diagnosis of chronic salpingitis, hydrosalpinx, etc., should be opened at once, for if cancer should be present, both ovaries must be removed. Unless it is unfit for radium application (myoma, etc.), the uterus should be left *in situ*.

The radiologic treatment should include both postoperative roentgen therapy and intracavitary radium application. Postoperative treatment includes (*a*) one intra-uterine application of radium, 1,500 mg. hr. or, if the uterus has been removed, 2,400 mg. hr. in the vagina; (*b*) roentgen treatment, (1) 3 × 400 r to each of two anterior and two posterior fields, (2) three months later, 2 × 400 r, and (3) after six months, 1 × 400 r, one treatment a day. Preoperative roentgen therapy should be administered whenever there is reason to believe cancer is present.

**Hemangioma of the Esophagus in Infancy.** Charles F. Ferguson and Lorye E. Hackworth. Arch. Otolaryng. **45:** 585–592, May 1947.

A seven-month-old boy with melena and hematemesis was found to have hemangioma of the esophagus. The diagnosis was made by esophageal biopsy. A daily dose of 200 r, measured in air, was given through a single posterior port (5 × 10 cm.) so placed as to cover the lower third of the esophagus and the cardiac end of the stomach, for a total of 1,000 r. The following factors were employed: 200 kv., 10 ma., a 50 cm. target-skin distance; a filter of 1.0 mm. aluminum and 0.5 mm. of copper with a half-value layer of 1.05 mm. of copper. After the five treatments the patient had no more vomiting and no recurrence of bleeding; his color improved remarkably. The reaction of the stools to guaiac rapidly became negative, and the red cell count remained 4,600,000 with a hemoglobin of 13.8 gm. Two years later a follow-up revealed no evidence of tumor, and the patient was free of symptoms.

**Hemangioma of Vertebra Associated with Spinal Cord Compression. Case Report.** D. Bernard Foster and Gilbert W. Heublein. Am. J. Roentgenol. **57:** 556–561, May 1947.

Vertebral hemangioma may be accompanied by the subjective symptoms and objective signs of compression of the spinal cord. The myelopathy in these cases is due to associated epidural hemangioma. The authors report a case in a man, aged 58, who complained of inability to walk. All the signs of compression of the spinal cord were present in the abdominal muscles and the lower extremities. Roentgen examination of the spine showed a hemangioma of the fourth dorsal segment extending into the laminae and proximal portions of the ribs bilaterally. Pantopaque myelography revealed a complete block at the level of the lower margin of the body of the fourth dorsal vertebra. Roentgen therapy was given, 3,500 r being delivered to a dorsal field and 2,000 r each to two anterior parasternal fields. The estimated tumor dose in the spinal canal was 3,526 r. The patient showed improvement beginning ten days after institution of radiation treatment. An excellent clinical recovery was obtained, and improvement was continuing nine months after the treatment was given. It is not felt that the delay of seven to twenty days before signs of beginning release of spinal cord compression appear following roentgen irradiation seriously impairs the patient's degree of ultimate recovery in the usual type of slowly progressing myelopathy such as shown in the case reported here. It is conceded that acute transverse myelitis occurring in the course of compression myelopathy from vertebral and epidural hemangioma is best treated by an immediate decompressive laminectomy.

CLARENCE E. WEAVER, M.D.

**Irradiation of Hyperplastic Lymphoid Tissue in the Nasopharynx.** Samuel J. Crowe and Edward M. Walzl. J. A. M. A. **134:** 124–125, May 10, 1947.

The presence of hypertrophied or chronically infected

lymphoid tissue in the nasopharynx has been recognized as the cause of many ills related to the upper air passages, as repeated colds, sinusitis, ear infection, and deafness. The purpose of irradiation of this lymphoid tissue is simply to remove it, and the authors state that one can expect improvement of any of the above conditions to the extent that the adenoids are the offending agent either by mechanical obstruction or by chronic infection.

Fortunately lymphoid tissue is extremely sensitive to irradiation with radium or x-rays, and doses that are too small to cause demonstrable effects on the mucous membrane, cartilage, or glands in the nasopharynx may yet cause disappearance of lymphoid tissue. The authors' radium applicator is in the form of a capsule at the end of an eight- to nine-inch slender rod. Filtration of 0.3 mm. stainless steel is used for radon and 0.3 mm. of monel metal for the radium salt. This filtration removes the beta radiation which, it is implied, is more likely to cause erythematous changes of the mucosa. The radium applicator contains 50 mg. of anhydrous radium sulfate.

A treatment time of about eight and one-half minutes to each side of the nasopharynx every ten days for three doses is recommended. Of course, visualization of the nasopharynx through a nasopharyngoscope is important to determine whether or not treatment is necessary and to know where to put the applicators. Local anesthesia with 10 per cent cocaine or pontocaine can be used.

The authors state that the mere presence of lymphoid tissue is no indication for treatment and that symptoms must be present also, such as deafness, otitis media, etc., due to obstructive phenomena of the eustachian tube. In children, to avoid recurrence, follow-up examinations should be done at least twice a year for two to three years. Aviators and submarine personnel suffering from aerotitis have been greatly benefited by this treatment (see Absts. in Radiology **47:** 547, 1946; **49:** 395, 1947, etc.). R. W. BYRN, M.D.
(University of Michigan)

**Effect of Radiation Therapy on the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer.** Erwin Levin, Anna Hamann, and Walter Lincoln Palmer. Gastroenterology **8:** 565–574, May 1947.

Experimental evidence has repeatedly shown that x-rays in sufficient quantity directed over the fundus and body of the stomach will produce temporary depression of gastric secretion. The present paper reports a clinical study. All of the patients were between thirty and sixty-three years of age and had uncomplicated duodenal ulcer demonstrated radiologically. Before radiation therapy, each was put on the usual hourly milk and cream and anti-acid regimen. At 9 P.M. the stomach was emptied with a large Ewald tube; a Levine tube was introduced and continuous suction was maintained for twelve hours. No antispasmodics or secretory depressants were given. Three continuous nightly aspirations were obtained on each patient before starting radiation therapy. Only those aspirations which showed no evidence of bile contamination were used in the study. Histamine tests, before, during, and after roentgen therapy, were done in the morning, using injections of 0.01 mg. per kilo body weight. The highest free acidity was considered to represent the maximum histamine response.

The night secretion was studied in 28 patients before therapy, in 9 while receiving therapy, and in 15 after therapy. In the last group the studies were continued from 14 to 150 days. All patients received a total depth dose of from 1,350 r to 1,710 r in daily treatments over a period of ten to fourteen days. The daily increment was 300 r as measured on the skin with backscatter through two portals measuring 13 by 13 cm. located over the body and fundus of the stomach anteriorly and posteriorly. One treatment per day through one portal was usually given. Technical factors were 200 kv.p.; 1 mm. Cu and 1 mm. Al filter; h.v.l. 1.3 to 1.5 mm. Cu; 20 ma.; 50 cm. F.S.D. Five such treatments were given to each anterior and each posterior portal.

The fasting nocturnal gastric secretion in 28 patients before therapy averaged 1,110 c.c. and the free acidity averaged 62 units. In the 9 patients studied during the course of therapy, there was a reduction in volume of acidity and free acidity during the first week of therapy in 7 and an increase in 2. In 14 of 15 patients studied after therapy, an average volume decrease of 47.4 per cent occurred. In one the volume increased, but the free acid disappeared. In all, marked reduction in free acid occurred, with complete anacidity in 13 of the 15. There was comparable reduction in gastric secretory response to histamine. In 14 of the 15 patients the depressive effect was still present after the ulcer crater could no longer be demonstrated radiologically. The length of the depressive effect is quite variable, however, in different patients. About one-third of the patients had transient roentgen sickness, but none showed changes in peripheral blood or evidence of visceral injury. B. S. KALAYJIAN, M.D.

**Irradiation Therapy of Benign Uterine Hemorrhage.** Ira H. Lockwood, Arthur B. Smith, and John W. Walker. South. M. J. **40:** 435–440, May 1947.

Radiation therapy for uterine hemorrhage caused by benign lesions has definite indications, and such hemorrhages should ideally be treated only after corroboration of the clinical diagnosis by biopsy and microscopic examination of the tissue removed. This is particularly true when the patients are treated in the hospital and especially when intra-uterine radium application is the method of choice.

Although the majority of patients suffering from benign uterine hemorrhage are in the age group forty to forty-five, such bleeding may occur after the menopause. In a survey of 179 cases of post-menopausal bleeding reported from the Johns Hopkins Hospital over a ten-year period, benign lesions were found to be responsible in 40 per cent.

Bleeding uterine myomas in persons under thirty-five, or in those over thirty-five desiring offspring, should be treated by conservative surgical methods. In patients over thirty-five years of age and those who are poor surgical risks, irradiation is indicated, but should not be done in cases of multiple subserous and submucous myomas. Good end-results have been reported in 98 per cent of those with functional uterine hemorrhage and in 94.5 per cent of those with bleeding uterine myomas (Schmitz: Am. J. Roentgenol. **33:** 819, 1935). The mortality was less than 1 per cent in both groups. Methods and results of treatment as published by numerous authorities are cited.

The majority of cases of benign uterine hemorrhage

treated by the present authors are in the age group forty to fifty-five, and the most common presenting symptom is profuse, prolonged menstrual periods. As a rule, these patients are treated by roentgen radiation, since it eliminates the necessity for hospitalization and it is felt that the menopausal symptoms are less severe than following radium therapy. However, radium is used in certain selected cases, particularly those in which prompt arrest of bleeding is imperative and in cases with an associated endocervicitis.

With roentgen irradiation, the authors give an average of 1,200 to 1,400 r (in air) to each of four pelvic areas in six weeks time. Technical factors are 200 kv., constant potential rectification, composite Thoraeus filter, 50 cm. skin-target distance, and 15 × 15-cm. ports. The radium dosage, depending upon the size of the uterus and the amount of associated endocervicitis is from 2,400 to 3,400 mg. hr., using 30 to 45 mg. of radium in an intra-uterine tandem with 0.5 mm. platinum filtration. The treatment of each patient must, however, be individualized. All factors involved must be considered, and the therapy regulated accordingly if satisfactory results are to be obtained.

BERT MALONE, M.D.

**Treatment of Tuberculous Salpingitis with Special Reference to X-ray Therapy.** Elliot Philipp. Proc. Roy. Soc. Med. **40:** 376–378, May 1947.

The author reports a series of 13 cases of tuberculous salpingitis treated by irradiation with favorable results. The doses given were small—a total of about 600 r in a course of twelve to eighteen treatments spread over six to nine weeks. A course can be repeated after an interval of several months without the production of a menopause. Small doses applied to the skin helped to close sinuses in some cases.

The following mechanism is offered to explain the beneficial results of x-ray therapy: "Small doses of x-rays traumatize tissues and destroy the most sensitive cells, which are lymphocytes. There is a general reaction to remove the destroyed cells and a very low-grade aseptic inflammation is set up which helps to overcome the tuberculous infection which previously had not been adequately combated."

M. WENDELL DIETZ, M.D.

## TECHNICAL CONSIDERATIONS

**Accuracy in Radon Work.** F. Ellis, W. A. Jennings, and S. Russ. Brit. J. Radiol. **20:** 181–189, May 1947.

In spite of the refinements of technic of filling radon seeds, there is considerable variation in the activity of individual seeds, though many users of radon do not realize this fact. A statistical study was made of seeds of various sizes and strengths, and the variations observed are discussed. These variations may be compensated for by individual measurement, and a suggested scheme of distributing the seeds is given which permits the administration of an evenly spaced dose.

SYDNEY J. HAWLEY, M.D.

**A System of Formulae and Curves Bearing on the Distribution of Energy in the Continuous Roentgen Spectrum.** R. H. de Waard. Acta radiol. **28:** 37–48, Feb. 28, 1947.

This paper is of a type which cannot be adequately abstracted. It presents a system of formulae from which can be derived the distribution of energy in the continuous spectrum of the radiation emitted by a roentgen tube acting under high tension of various forms, with or without filtration. The formulae are based on a simple assumption suggested by experiments published by Kulenkampff (Ann. d. Physik. **97:** 79, 1926), namely, that the distribution of energy is essentially given by a system of parallel straight lines.

The energy-distribution in question can be largely characterized by the minimum wavelength $\lambda_0$ and the wavelength $\lambda_m$ of maximum intensity A simple method is given by which these two wave lengths can be determined with the help of some curves. This method is illustrated by two examples of some practical importance

## RADIOACTIVE ISOTOPES

**Isotopes in Medical Research.** J. H. Lawrence. J. A. M. A. **134:** 219–225, May 17, 1947.

This article is a résumé of the important radioactive isotopes available at the present time, the significant characteristics of these substances, and the methods in which they may be used in various phases of medical work.

Isotopes can be used as therapeutic agents, being substituted for x-rays and radium, or they may be employed as tracer substances in metabolic studies. Two methods of detecting isotopes are described: (1) autoradiographic, in which an animal containing radioactive material is sectioned and the sections are applied to photographic plates; (2) the *in vitro* method, in which specimens of body fluids are collected, weighed, ashed, and measured for radioactive material.

The possibility of discovering a radioactive isotope that will selectively localize in neoplastic tissue is mentioned. Special emphasis is placed upon the health hazards assumed by physicians who handle radioactive materials.

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**Medical Use of Radioactive Isotopes. I. Radioactive Isotopes in Hematologic Disturbances and Neoplasms.** Byron E. Hall and Charles H. Watkins. Am. J. M. Sc. **213:** 621–628, May 1947. **II. Radio-Iodine and the Thyroid.** F. Raymond Keating, Jr. Ibid, pp. 628–631.

These two papers review the work that has been reported by others on the use of radioactive phosphorus in the blood dyscrasias and of radio-iodine in the study of the thyroid and in the treatment of thyroid cancer. Brief mention is also made of radiostrontium, radioiron, and radiosodium. Full bibliographies are appended.

**Medical Applications of Artificial Radioactive Isotopes.** Kenneth A. Evelyn. Canad. M. A. J. **56:** 547–554, May 1947.

After a general discussion of radioactive isotopes, the author takes up the applications of artificial radioactive isotopes to medical research, the difficulties in application, the present status of tracer research, the use of artificial radio-elements for internal radiation, the use

of artificial radioactive isotopes as substitutes for radium, and the health hazards involved in the use of artificial radioactive isotopes.

**Radio-Autographic Studies of the Distribution of Lewisite and Mustard Gas in Skin and Eye Tissues.** Dorothy J. Axelrod and Joseph G. Hamilton. Am. J. Path. **23:** 389–411, May 1947.

The distribution of two war gases, mustard and lewisite, labeled with radioactive sulfur ($S^{35}$) and radioactive arsenic ($As^{74}$), respectively, in skin and eye tissues has been studied by the radioautographic technic. In all of the autographs, mustard gas penetrated the skin much more deeply than lewisite with a corresponding exposure. This deep penetration could explain the great destruction and deep burns resultant from exposure to mustard gas. In both the mustard and lewisite studies an accumulation of these two materials was noted in and around blood vessels. With destruction of blood vessels and subsequent local anemia, one would expect slow healing of the affected skin area to ensue, which is a characteristic feature of these burns.

In rabbit eyes exposed to mustard gas this material was fixed primarily in the cornea, with a small amount in the conjunctiva, and a very small amount in the iris and lens.

The authors' method of making the radioautographic studies is described. By this method it is possible to determine the radioactivity present in small regions of tissue sections, *i.e.*, in blood vessels, hairs, hair follicles, and accessory glands of the skin.

## EFFECTS OF RADIATION

**Induction of Ovarian Tumors in Mice by X-Rays.** J. Furth and M. C. Boon. Cancer Research **7:** 241–245, April 1947.

Following irradiation of four- to six-week-old mice with 87 r, 175 r, or 350 r, ovarian tumors began to appear when the mice were about eleven months of age. The frequency of these neoplasms increased with time and in almost every mouse that lived seventeen months a unilateral or bilateral ovarian growth developed, irrespective of the dose of irradiation.

All mice were F1 hybrids of Rf females and Ak males and were thus genetically alike. This stock was used because it has a low incidence of neoplastic diseases, because it appears relatively resistant to the usual intercurrent infections, and because of its longevity. The factors of irradiation were as follows: 140 kv., 5 ma., 30 cm. target-skin distance, with an inherent filtration of 1 mm. aluminum. The mice were "painted" twice a week with methylcholanthrene.

The ovarian growths are compared as to pathogenesis and autonomous character with the hyperplastic nodules that result from implantation of normal ovaries into the spleens of castrated mice. It is concluded that the latter are not autonomous neoplastic growths (although they sometimes give rise to true neoplasms); while the x-ray-induced ovarian growths, on the contrary, are readily transplantable autonomous growths.

The factors necessary for the induction of ovarian growths in mice and the bearing of the observations made on the general problems of carcinogenesis are discussed

**On the Mechanism of Shock or General Reaction of Cells and Organisms to Injury (Outline of a Working Hypothesis).** Jørgen E. Thygesen. Acta radiol. **28:** 1–13 Feb. 28, 1947.

According to the working hypothesis outlined by the author, the general as well as the local defense of the organism is closely associated with the amine metabolism and vegetative nerve processes. No matter whether a local injury to the tissues is produced by morbid processes or by intentional measures, *e.g.*, roentgen irradiation, a general effect will appear, threatening the existence of the organism. This reaction is connected, among other things, with the processes of regeneration, by which the organism tries to counteract the local necrobiosis.

The central point in the mechanism of injury to the cell is the change in its protein structure, which governs its chemical exchanges. The function of the adrenal cortex plays a determining role in the defensive capacity of the organism, as desoxycorticosterone (adrenocortical hormone) stimulates the synthesis of protein by the cells and thus tends to normalize the injured protein structure. Acute states of shock are associated with cortin deficiency or relative adrenocortical insufficiency on account of the incapacity of the organ for immediate adjustment to the increased requirement. Roentgen intoxication represents a protracted state of shock which, according to theory and the experiments of the author, is amenable to treatment with desoxycorticosterone or histamine.

**Radioactive Emanations: Their Nature, Mechanism of Action, Biological Effects and Tolerance Limits.** Bradford N. Craver. J. Indust. Hyg. & Toxicol. **29:** 196–200, May 1947.

The characteristics of the various common types of radiation produced by atomic disruption are reviewed. The nature of the biological changes that they produce is discussed as well as the mechanism of their production. The curie and the roentgen are defined and human tolerance limits stated in terms of those units.

**Provisional Calculation of the Tolerance Flux of Fast Neutrons.** J. S. Mitchell. Brit. J. Radiol. **20:** 177–180, May 1947.

Calculations of the theoretical flux of fast neutrons equivalent to the 0.1 r per day tolerance dose were made by applying Placzek's theory of the slowing down of fast neutrons by elastic collisions with atomic nuclei (Phys. Rev. **69:** 423, 1946). These calculations suggest that the flux of fast neutrons corresponding in biological effect to a dose of 0.1 r of the usual filtered gamma radiation from radium of approximate mean energy 0.8 Mev., delivered in eight hours, has the approximate constant value of 85 neutrons per square centimeter per second for neutrons of energy 2–20 Mev. Because of the lack of experimental evidence of the biological effects of neutrons, it is probably safer, however, to use 20 neutrons per sq. cm. per second as the tolerance dose. This value can be doubled for neutrons of energy 0.5 Mev.

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